World Review of Nutrition and Dietetics

Volume
126

Nutrition and Growth

Yearbook 2023

Editors
Raanan Shamir
Berthold Koletzko
Moshe Phillip
Dominique Turck

Nutrition and Dietetics

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RESEARCH

World Review of Nutrition and Dietetics

Vol. 126

Series Editor

Berthold Koletzko Munich

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2023

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Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and PubMed/MEDLINE.

www.karger.com
Printed on acid-free and non-aging paper (ISO 9706)
ISSN 0084–2230
e-ISSN 1662–3975
ISBN 978–3–318–07056–9
e-ISBN 978–3–318–07246–4

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Published online: March 22, 2023

Phillip M, Turck D, Shamir R (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp IX (DOI: 10.1159/000527946)

Preface

Linear growth, weight gain, and body composition are affected by a complex variety of factors, with nutrition being one of the most important contributors. Yet, the mechanisms by which nutrition affects growth is not completely understood. In this yearbook, we are trying to uncover the interplay between nutrients and the endocrine systems via manuscripts describing different clinical conditions and diagnoses covering various aspects of the relationship between nutrition and growth.

Tremendous research efforts are invested all over the world in trying to understand the mechanisms leading to growth failure, the proper diet composition for optimal child growth, and the appropriate diet for children suffering from undernutrition or malnutrition at all age groups during the growth period. These efforts may help to further develop more effective nutritional interventions for improving growth in children.

In this book, specialists in nutrition and growth gave their best to choose manuscripts published during the last year that provide a significant contribution to our knowledge base. The authors of this book have chosen a limited number of peer-reviewed manuscripts that were published between July 2021 and June 2022 and added their comments on these manuscripts. We are sure that there are more important studies, and apologize for not being able to include a larger number because of limited space.

We do hope, however, that this compilation will stimulate the readers to look for more manuscripts in the field of nutrition and growth, and that our comments will serve as a "food for thought" that will lead to increased interest and to more research in the field.

We wish to extend our gratitude to our associate editors for the contribution of their valuable time in sharing their knowledge and expertise with our readers.

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Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 1–16 (DOI: 10.1159/000527935)

Malnutrition and Catch-Up Growth during Childhood and Puberty

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Introduction

In 2020, approximately 149.2 million children, or 22%, of all children under 5 years of age across the globe were estimated to be affected by stunting, and 45.4 million children under 5 by wasting, of whom 13.6 million were severely wasted [1]. Although the rates of both stunting and wasting have been significantly reduced over the past couple of decades, these numbers are still staggering. According to the WHO, the number of people affected by hunger globally have increased by 150 million since the outbreak of COVID-19 [2]. Amidst climate changes, economic instability, and growing inequalities, achieving the global targets of reducing the number of children with stunting to 104 million by 2025 and to 87 million by 2030 seems more challenging than ever.

This chapter reviews the most recent data on childhood malnutrition and catch-up growth, published between July 1, 2021, and June 30, 2022, and addresses several topics: (a) etiology and mechanisms of malnutrition in children, (b) adolescent nutrition (*Lancet* Series), (c) interventions, and (d) late outcomes of malnutrition.

Key articles reviewed for this chapter

Etiology and Mechanisms of Malnutrition in Children

Determinants of malnutrition among children: a systematic review
Katoch OR
Nutrition 2022;96:111565

Greater male vulnerability to stunting? Evaluating sex differences in growth, pathways and biocultural mechanisms
Thompson AL
Ann Hum Biol 2021;48:466–473

Adolescent Nutrition, *Lancet* Series

Nourishing our future: the *Lancet* Series on adolescent nutrition
Patton GC, Neufeld LM, Dogra S, Frongillo EA, Hargreaves D, He S, Mates E, Menon P, Naguib M, Norris SA
Lancet 2022;399(10320):123–125

Nutrition in adolescent growth and development
Norris SA, Frongillo EA, Black MM, Dong Y, Fall C, Lampl M, Liese AD, Naguib M, Prentice A, Rochat T, Stephensen CB, Tinago CB, Ward KA, Wrottesley SV, Patton GC
Lancet 2022;399(10320):172–184

Food choice in transition: adolescent autonomy, agency, and the food environment
Neufeld LM, Andrade EB, Ballonoff Suleiman A, Barker M, Beal T, Blum LS, Demmler KM, Dogra S, Hardy-Johnson P, Lahiri A, Larson N, Roberto CA, Rodríguez-Ramírez S, Sethi V, Shamah-Levy T, Strömmer S, Tumilowicz A, Weller S, Zou Z
Lancet 2022;399(10320):185–197

Strategies and interventions for healthy adolescent growth, nutrition, and development
Hargreaves D, Mates E, Menon P, Alderman H, Devakumar D, Fawzi W, Greenfield G, Hammoudeh W, He S, Lahiri A, Liu Z, Nguyen PH, Sethi V, Wang H, Neufeld LM, Patton GC
Lancet 2022;399(10320):198–210

Intervention

Small-quantity lipid-based nutrient supplements for the prevention of child malnutrition and promotion of healthy development: overview of individual participant data meta-analysis and programmatic implications
Dewey KG, Stewart CP, Wessells KR, Prado EL, Arnold CD
Am J Clin Nutr 2021;114(Suppl 1):3S–14S

Effectiveness of community nutrition-specific interventions on improving malnutrition of children under 5 years of age in the Eastern Mediterranean region: a systematic review and meta-analysis
Ghodsi D, Omidvar N, Nikooyeh B, Roustaee R, Shakibazadeh E, Al-Jawaldeh A
Int J Environ Res Public Health 2021;18:7844

Ready-to-use therapeutic food (RUTF) containing low or no dairy compared to standard RUTF for children with severe acute malnutrition: a systematic review and meta-analysis
Potani I, Spiegel-Feld C, Brixi G, Bendabenda J, Siegfried N Bandsma RHJ, Briend A, Daniel AI
Adv Nutr 2021;12:1930–1943

Worldwide evidence about infant stunting from a public health perspective: a systematic review
Rueda-Guevara P, Botero Tovar N, Trujillo KM, Ramírez A
Biomédica 2021;41:541–554

Effect of oral nutritional supplementation on growth in children with undernutrition: a systematic review and meta-analysis
Zhang Z, Li F, Hannon BA, Hustead DS, Aw MM, Liu Z, Chuah KA, Low YL, Huynh DTT
Nutrients 2021;13:3036

Effective interventions to address maternal and child malnutrition: an update of the evidence
Keats EC, Das J, Salam RA, Lassi ZS, Imdad A, Black RE, Bhutta ZA
Lancet Child Adolesc Health 2021;5:367–384

Birth length is the strongest predictor of linear growth status and stunting in the first 2 years of life after a preconception maternal nutrition intervention: the children of the Women First trial
Krebs NF, Hambidge KM, Westcott JL, Garcés AL, Figueroa L, Tshefu AK, Lokangaka AL, Goudar SS, Dhaded SM, Saleem S, Ali SA, Bauserman MS, Derman RJ, Goldenberg RL, Das A, Chowdhury D, the Women First Preconception Maternal Nutrition Study Group
Am J Clin Nutr 2022;116:86–96

Late Outcomes of Childhood Malnutrition

Body composition of adults with a history of severe acute malnutrition during childhood using the deuterium dilution method in eastern DR Congo: the Lwiro Cohort Study
Mwene-Batu P, Wells J, Maheshe G, Hermans MP, Kalumuna E, Ngaboyeka G, Chimanuka C, Owino VO, Macq J, Lukula M, Dramaix M, Donnen P, Bisimwa G
Am J Clin Nutr 2021;114:2052–2059

Liver fat in adult survivors of severe acute malnutrition
Thompson DS, Royal-Thomas TYN, Tennant IA, Soares DP, Byrne CD, Forrester TE, Gluckman PD, Boyne MS
Sci Rep 2022 7;12:3690

Determinants of malnutrition among children: a systematic review

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Nutrition 2022;96:111565

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Comments: Despite considerable progress in reducing undernutrition and related stunting and wasting in the past 2 decades, as of 2020 there are still 149 million children under the age of 5 years affected with stunting worldwide. Numerous factors are related to childhood malnutrition, having a direct or indirect effect on child nutrition in developing countries. This systematic review and meta-analysis aim to determine the most consistent factors related to childhood stunting in the past decade by reviewing relevant studies published between 2012 and 2021. The review included 37 studies (each including a population of between 100 and 798,961 children) from various countries worldwide. The study found that the most significant determinants of childhood malnutrition were maternal education, household income, maternal nutritional status, age of the child, availability of sanitation facilities at home, size of family, birth order in the family, and the child's birth weight. Interestingly, older children were found to be at higher risk for malnutrition and stunting than younger children. Although this meta-analysis did not exclude studies with suboptimal design, the large numbers and the diversity of social, geographic, and ethnic backgrounds in the studies included validate its findings.

Greater male vulnerability to stunting? Evaluating sex differences in growth, pathways and biocultural mechanisms

Thompson AL[1,2,3]

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Ann Hum Biol 2021;48:466–473

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https://pubmed.ncbi.nlm.nih.gov/35105202/

Comments: Sex and gender have implications on health outcomes throughout the course of life, and across the globe. Sex can affect disease susceptibility, progression, and prognosis via genetic, immune, and hormonal pathways. Moreover, gender roles, norms and perceptions, gender-based differences in access to resources and health services, and differences in health behaviors also strongly influence health outcomes. This review presents evidence regarding the differences in susceptibility to stunting between boys and girls, and discusses the many ways in which both sex and gender influence

stunting in children. The review addresses sex-based differences in sensitivity to infectious diseases, differences in requirements for growth, in environmental exposures, and in care practices, and aims to integrate the biological and social pathways influencing growth, from the prenatal period throughout childhood. It highlights the need to tailor interventions aimed at stunting prevention according to the child's specific environmental and social surroundings.

Adolescent Nutrition, *Lancet* Series

Nourishing our future: the *Lancet* Series on adolescent nutrition

Patton GC[1,2], Neufeld LM[3], Dogra S[4], Frongillo EA[6], Hargreaves D[7], He S[5], Mates E[8], Menon P[9], Naguib M[10], Norris SA[11,12]

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Lancet 2022;399(10320):123–125
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Nutrition in adolescent growth and development

Norris SA[1,2], Frongillo EA[4], Black MM[6,7], Dong Y[8], Fall C[3], Lampl M[9], Liese AD[5], Naguib M[10], Prentice A[11,12], Rochat T[1], Stephensen CB[13], Tinago CB[14], Ward KA[3,12], Wrottesley SV[1], Patton GC[15]

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Food choice in transition: adolescent autonomy, agency, and the food environment

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Lancet 2022;399(10320):185–197
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Strategies and interventions for healthy adolescent growth, nutrition, and development

Hargreaves D[1], Mates E[2], Menon P[3], Alderman H[4], Devakumar D[5], Fawzi W[6], Greenfield G[7], Hammoudeh W[8], He S[9], Lahiri A[10], Liu Z[12], Nguyen PH[3], Sethi V[11], Wang H[12], Neufeld LM[13], Patton GC[14]

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Lancet 2022;399(10320):198–210

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https://pubmed.ncbi.nlm.nih.gov/34856192/

Comments: Adolescents are not simply younger adults or older children; they are unique, with specific needs, risks, attitudes, and opportunities related to dietary intake and food choices. Like other age groups, adolescents face various nutritional problems, including micronutrient deficiencies and food insecurity, low weight, short stature, as well as obesity and metabolic disorders. However, adolescence is a unique phase of life, in several ways. First, the linear growth rate during adolescence is greater than in any other stage of life, excluding the first year of life. Hence, adolescence is a nutrition-sensitive phase of growth, in which the benefits of good nutrition extend to many other physiological systems. Second, adolescence is the time of transition from primary dependence on caregivers to an increasing number of roles and responsibilities related to food purchase, preparation, and consumption, presenting an opportunity to establish healthy eating habits. Furthermore, adolescents differ from younger children in exercising greater choice over their nutrition, as they have strong opinions regarding their eating choices, and the factors that may motivate them to change. Adolescents in the current generation, more than any before, have concerns about the harmful impacts of the food industry on the environment.

A new *Lancet* Series provides a comprehensive overview on the existing data on adolescent nutrition and sets out the challenges and opportunities for addressing healthy adolescent nutrition and development. This series highlights the neglect in policy, programming, and research means regarding this age group compared with other age groups. The series mentions several research gaps in this field and highlights the need of further research and data collection. It also recommends that adolescent nutrition promotion and interventions should occur in partnership with young people and be framed within broader commercial, cultural, and ecological contexts.

The series includes an introduction (Patton et al.) followed by 3 parts:

1. "Nutrition in adolescent growth and development," by Norris et al., which synthesizes the understanding of adolescent biological development and its relationship with nutrition.

2. "Food choice in transition: adolescent autonomy, agency, and the food environment," by Neufeld et al. This paper describes patterns of dietary intake among adolescents, maps how food choices can be influenced by unique features of adolescent development, and ends with a series of key considerations for policies, programs, and further research.
3. "Strategies and interventions for healthy adolescent growth, nutrition, and development," by Hargreaves et al. This paper discusses how a nutrition-focused strategy based on adolescent interventions offers new options for coping with the global burden of obesity, undernutrition, and climate change.

Intervention

Small-quantity lipid-based nutrient supplements for the prevention of child malnutrition and promotion of healthy development: overview of individual participant data meta-analysis and programmatic implications

Dewey KG, Stewart CP, Wessells KR, Prado EL, Arnold CD

Institute for Global Nutrition and Department of Nutrition, University of California, Davis, Davis, CA, USA

Am J Clin Nutr 2021;114(Suppl 1):3S–14S

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https://pubmed.ncbi.nlm.nih.gov/34590696/

Comments: The first ready-to-use therapeutic food (RUTF) for treating severe malnutrition, based on fat-based matrix and micronutrients, was developed in the late 1990s. This technology allows the product to have a low water content, which inhibits the growth of bacteria without refrigeration. Small-quantity lipid-based nutrient supplements (SQ-LNSs) for preventing malnutrition in vulnerable populations were later developed, based on the same type of food-based matrix as RUTF, but using a much smaller quantity of food, typically about 4 teaspoons (about 100 kcal) per day. SQ-LNSs provide energy, protein, essential fatty acids, and multiple micronutrients.

This meta-analysis by Dewey et al., which included 14 randomized controlled trials (RCTs), and more than 37,000 participants, aimed to study the effects of SQ-LNSs provided to children 6–24 months of age on various outcomes. This meta-analysis showed that intervention with SQ-LNSs had significant benefits in reducing the prevalence of stunting, wasting, and underweight; improved cognitive and motor development outcomes; and prevented iron deficiency and anemia. Beneficial effects of SQ-LNSs were shown in heterogenous study designs and settings (various geographical regions, levels of stunting burden, malaria prevalence, sanitation, water quality, duration of supplementation, and compliance with SQ-LNSs). The benefits of SQ-LNSs were greater in populations with a higher stunting burden, higher anemia prevalence, and lower socioeconomic status, and among acutely malnourished children.

According to the results of this meta-analysis, the authors suggest intervention with SQ-LNSs in more vulnerable populations who have greater potential to benefit by it

(populations with lower socioeconomic status who are at greater risk of malnutrition and anemia). The authors also suggest that a greater impact of SQ-LNSs may be obtained by combination with other interventions such as prevention and control of infections and inflammation, improving access to health care, and promoting early child development.

Effectiveness of community nutrition-specific interventions on improving malnutrition of children under 5 years of age in the Eastern Mediterranean region: a systematic review and meta-analysis

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Int J Environ Res Public Health 2021;18:7844

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https://pubmed.ncbi.nlm.nih.gov/34360137/

Comments: The Eastern Mediterranean Region (EMR) comprises 22 countries extending from Pakistan in Southern Asia to Morocco in North Africa. These countries are very heterogeneous in their ecology, economy, and healthcare services. Many of these regions are inflicted by war and conflicts, therefore resulting in poverty and poor nutrition. Several reviews, which included children from the EMR, have reported different rates of wasting, stunting, and underweight across these countries, and show that the 2 opposing nutrition-related diseases, malnutrition and obesity, paradoxically coexist. Numerous efforts have been made to reduce child malnutrition in the region. However, published information is scarce. This systematic review and meta-analysis by Ghodsi et al. aimed to evaluate the effectiveness and the cost-effectiveness of community-based nutrition-specific interventions on the nutritional status of children under 5 years of age in the EMR.

The systematic review yielded only 8 RCTs that met the inclusion criteria, 7 from Pakistan and 1 from Iran. Only one study reported the cost-effectiveness of nutrition-specific interventions. The most common strategies used for management of child malnutrition in the EMR countries were nutrition education (including counseling on child complementary feeding) and cash-based interventions. Only 4 studies were included in the meta-analysis and showed that the different interventions had resulted in a significant improvement in weight-for-height z-score. No improvement was seen in height-for-age z-score.

The authors conclude that the scarcity of available studies in the region and their heterogeneity make it difficult to conclude which type of intervention is the most effective. The authors further note that although the results of the meta-analysis indicate that nutritional education and supplementary food distribution may have favorable effects on the weight and height status of children, these strategies obviously cannot eliminate poverty and poor sanitation, which are the underlying causes of child malnutrition. Poverty and poor sanitation should be addressed through appropriate policies and interventions.

Ready-to-use therapeutic food (RUTF) containing low or no dairy compared to standard RUTF for children with severe acute malnutrition: a systematic review and meta-analysis

Potani I[1,2,3,4], Spiegel-Feld C[2], Brixi G[5], Bendabenda J[6], Siegfried N[7], Bandsma RHJ[1,2,3,4,8], Briend A[9,10], Daniel AI[1,2,3]

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Adv Nutr 2021;12:1930–1943
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Comments: Ready-to-use therapeutic food (RUTF) was developed for nutritional rehabilitation of children with severe acute malnutrition (SAM). Current guidelines, as specified by WHO, state that at least 50% of protein in RUTF should come from milk products, due to their higher protein quality as compared to other protein sources. However, milk proteins are more costly ingredients than nonmilk proteins. Hence, RUTF containing less dairy may be an attractive lower-cost treatment alternative for SAM.

The aim of this systematic review and meta-analysis by Potani et al. was to compare the effectiveness of RUTF containing nondairy sources of protein, or less than 50% of protein from dairy products, with standard RUTF in children aged 6 months or older with SAM.

The meta-analysis included 6 RCTs which met the inclusion criteria, with a total sample of 6,356 children, examining the effect of 7 different intervention RUTF recipes. The results of the meta-analysis showed that nondairy or lower-dairy RUTF resulted in less weight gain, lower recovery, and lower weight-for-age z-scores near program discharge. Other anthropometric measures (height-for-age z-scores, weight-for-height z-score, and mid-upper-arm circumference), mortality, time to recovery, and adherence to the program did not differ between groups.

This systematic review has several important limitations. First, all the studies included in this review were of short term and followed participants only until discharge or shortly thereafter. Studies with longer follow-up durations are also needed to fully understand the effects of alternative versions of RUTF on different outcomes, like anthropometry, body composition, the gut microbiota, child development, and overall health. A second limitation is the heterogeneity of the low- or no-dairy RUTF formulations that were included in the meta-analysis. The differences in the nutritional composition, and in protein source and quality, make it difficult to interpret the results and define the ideal nutritional composition of alternative RUTF. A third limitation is that this systematic review does not include a cost-effectiveness evaluation. Although low- or no-dairy RUTF formulations could possibly lower SAM treatment costs, if these alternative RUTF result in worse outcomes or longer treatment duration, the total costs may be similar or even higher. The authors emphasize the need in continuing the research aimed to optimize more cost-effective versions of RUTF. They further suggest whey protein, which is a lower-cost dairy alternative to skimmed-milk powder, as a future direction of research.

Worldwide evidence about infant stunting from a public health perspective: a systematic review

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Comments: Linear growth rate is a strong indicator of overall child development during the first years of life and of inequalities in child development. The aim of this systematic review by Rueda-Guevara et al. was to identify and describe worldwide evidence on prevention, nutritional interventions, and intersectoral collaboration efforts against stunting in infants under 2 years of age.

This extensive systematic review included 231 studies, most of which were interventional studies and cross-sectional studies. Most of the studies were conducted in low- and middle-income countries (Africa, Southeast Asia, and the Americas WHO regions). The most frequent topics were stunting prevention, intersectoral collaboration, and nutritional interventions, which were targeted at 3 main populations: pregnant women, babies from birth to 6 months, and infants from 6 months to 2 years. The most frequent interventions were prebirth care (i.e., promotion and assessment of adequate gestational weight-gain), nutritional counseling for the mother and the child (i.e., counseling on breastfeeding and complementary feeding), and counseling on micronutrient supplementation.

This systematic review may be useful for informing public health policy decision-makers and researchers, as it summarizes, interprets, and highlights knowledge gaps of the existing literature regarding stunting prevention in infants.

Effect of oral nutritional supplementation on growth in children with undernutrition: a systematic review and meta-analysis

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Nutrients 2021;13:3036

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Comments: Many children worldwide experience undernutrition and growth faltering. Poor growth due to undernutrition is more commonly the result of multiple nutrient deficiencies and not a single-nutrient deficiency. Oral nutritional supplements (ONS) are liquid, semisolid, or powder formulas containing proteins and at least one nonprotein source of energy (carbohydrate and/or fat) in balanced amounts, as well as a wide range of micronutrients. Hence, ONS may be an effective nutrition intervention approach to tackle growth faltering in at-risk or undernourished children.

The systematic review and meta-analysis by Zhang et al. summarizes the evidence of the effects of ONS on growth in undernourished, or those at nutritional risk, healthy children aged 9 months to 12 years.

This systematic review included 11 RCTs (2,287 children) that met the inclusion criteria. The results of the meta-analysis showed that the provision of ONS had significant positive effects on weight and height gain compared to the control groups who received usual diet, placebo, or dietary counseling. Longitudinal analyses of up to 90 days of follow-up showed that the gains in weight were seen earlier than the gains in height: while greater gains in weight indices were reported from 30 days onward, a trend toward greater height gains were reported at 90 days. This suggests that nutritional supplementation in undernourished children should be given for at least 3 months to promote height catch-up.

The meta-analysis highlights several limitations and research gaps in the existing literature. First, no RCTs were available for children above 12 years of age, although catch-up growth occurs not only in early childhood but also during puberty. Second, most of the studies were of short duration (up to 90 days). Third, there was a big heterogeneity in the age ranges of the children, the ONS nutritional composition, the duration of the intervention, dosing, and compliance. This heterogeneity makes it difficult to conclude what is the ideal nutritional composition of ONS and the most effective setting for the intervention.

Further studies are needed to evaluate the effect of ONS on promoting catch-up growth, with longer follow-up duration (90 days or more), and including children above 12 years of age, particularly those going through puberty.

Effective interventions to address maternal and child malnutrition: an update of the evidence

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Lancet Child Adolesc Health 2021;5:367–384

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Comments: This is an update of the evidence base of interventions to address global maternal and child nutrition challenges since the last such review in 2013 [3]. The review focused on emerging and new evidence on interventions such as antenatal multiple micronutrient supplements with benefits of reducing the risk of low birth weight and babies born small-for-gestational-age, with consequent impacts on stunting and human development. The evidence strengthened on the benefits of supplementary foods in food-insecure settings and community-based approaches with the use of locally produced supplementary and therapeutic food to manage children with acute malnutrition. While relatively few strategies had looked at affordable and effective complementary feeding options, the evidence related to preventive small-quantity lipid-based nutrient supplements for child growth among children aged 6–23 months was strong and positive. For the prevention and management of childhood obesity, integrated interventions (e.g., diet, exercise, and behavioral therapy) were effective, but few had been evaluated in low- and middle-income country settings. The review also assessed evidence-based indirect nutrition strategies, such as malaria prevention, preconception care, family planning, water, sanitation, and hygiene promotion, delivered inside and outside the healthcare sector, which also provide important nutritional benefits. A lot more work is needed around scaling up and delivery platforms for nutrition interventions, especially in neglected areas like school-age and young adolescents [4].

Birth length is the strongest predictor of linear growth status and stunting in the first 2 years of life after a preconception maternal nutrition intervention: the children of the Women First trial

Krebs NF[1], Hambidge KM[1], Westcott JL[1], Garcés AL[2], Figueroa L[2], Tshefu AK[3], Lokangaka AL[3], Goudar SS[4], Dhaded SM[4], Saleem S[5], Ali SA[5], Bauserman MS[6], Derman RJ[7], Goldenberg RL[8], Das A[9], Chowdhury D[9], the Women First Preconception Maternal Nutrition Study Group

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Am J Clin Nutr 2022;116:86–96

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Comments: These are important data from the multicountry Women First trial showing that nutritional supplementation initiated prior to conception or early in pregnancy and continued until delivery was associated with significantly greater length at birth and 6 months of age compared with control infants.

The Women First trial was conducted in several low-income population settings in the Democratic Republic of Congo, Guatemala, India, and Pakistan. Longitudinal models evaluated intervention effects on infants' growth trajectory from birth to 24 months of age, with additional modeling used to identify adjusted predictors for growth trajectories and outcomes at 24 months.

A large proportion (95% of original live births) of infants were evaluated at 24 months of age. While stunting rates were still high at 24 months of age (>62%), the length-for-age z-score (LAZ) trajectory was better with both preconception and pregnancy supplementation (with adjusted mean differences of 0.19 SD [95% CI: 0.08, 0.30; $p < 0.001$] and 0.17 SD [95% CI: 0.07, 0.27; $p < 0.001$]) compared with the control group, respectively. The strongest predictors of LAZ at 24 months were birth LAZ < -2 and < -1 to ≥ -2, with adjusted mean differences of -0.76 SD (95% CI: -0.93, -0.58; $p < 0.001$) and -0.47 SD (95% CI: -0.56, -0.38; $p < 0.001$), respectively. This study underscores the importance of maternal nutrition in pregnancy for improving fetal and infant health and nutrition (in addition to substantial benefits for the mother herself). Similar findings are notable from studies of exemplars of reduction in stunting across countries with investments in indirect interventions in poverty reduction, maternal education, health and nutrition programs [5], and in malaria endemic areas, investments in reducing malaria burden in pregnancy [6].

Body composition of adults with a history of severe acute malnutrition during childhood using the deuterium dilution method in eastern DR Congo: the Lwiro Cohort Study

Mwene-Batu P[1,2,3,4], Wells J[5], Maheshe G[1,4], Hermans MP[6], Kalumuna E[4], Ngaboyeka G[1], Chimanuka C[1], Owino VO[7], Macq J[8], Lukula M[1], Dramaix M[2], Donnen P[2], Bisimwa G[1,3]

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Am J Clin Nutr 2021;114:2052–2059

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Liver fat in adult survivors of severe acute malnutrition

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Sci Rep 2022;12:3690

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https://pubmed.ncbi.nlm.nih.gov/35256686/

Comments: Acute malnutrition is a major public health problem in low- and middle-income countries and a leading cause of death in children aged under 5 years in these regions. Over the past decades, early intervention and treatment with RUTFs has lowered immediate mortality from acute malnutrition and increased the number of malnutrition survivors. These survivors may experience late adverse effects such as stunted growth and mental and physical disability, and have a higher risk of developing cardiometabolic diseases in adulthood. Both of the above studies focus on the late outcomes of

acute malnutrition in adults, in an attempt to clarify the metabolic mechanisms leading to increased risk for noncommunicable diseases. The first study (Mwene-Batu et al.) examined body composition (BC) in adults who were exposed to acute malnutrition compared to the BC of age-, sex- and BMI-matched controls from the same communities, who had not been exposed to malnutrition. The authors found similarly normal BC in both groups, except for lower fat-free mass in men previously exposed to malnutrition, and attributed this finding to the shorter stature in this group. The second study (Thompson et al.) investigated differences in liver fat in survivors of severe wasting, versus survivors of edematous malnutrition and community controls. The authors found that after adjusting for birth weight, survivors of severe wasting had more liver fat than survivors of edematous malnutrition. No differences in liver fat were found between both group of survivors and controls. These results are in line with previous studies showing a greater susceptibility for cardiovascular disease in survivors of severe wasting than in survivors of kwashiorkor. These studies highlight the need to continue monitoring adults who were exposed to malnutrition in childhood and further study the sources of the double burden of malnutrition.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 17–31 (DOI: 10.1159/000527936)

Stunting of Growth in Developing Countries

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Introduction

Stunting, namely length-for-age more than 2 standard deviations below the median for the World Health Organization growth reference standards, is the most common form of childhood malnutrition. It is an indicator of chronic malnutrition that predicts an increased risk of death in childhood as well as being associated with adverse health and cognitive outcomes during childhood that persist into adulthood. In 2020, over 149 million children under 5 years were stunted [1]. Many low- and middle-income countries (LMICs) have committed to the sustainable development goal target of eliminating childhood malnutrition by 2030 [2], yet with the current global trends, it is unlikely that this will be achieved. Innovative and accelerated efforts are therefore required to enable many LMICs to meet the 2030 global nutrition targets. The ongoing impact of the COVID-19 pandemic, coupled with worsening food security, economic crises, climate change, and conflict, has undoubtedly reversed any gains that had been made prepandemic [3]. While about one quarter of all COVID-related childhood deaths are attributed to wasting [4] (severe acute malnutrition [SAM]), the impact of childhood stunting is yet to be fully understood [5]. In addition, although the impact of socioeconomic inequalities on health outcomes is well-described [6], the complexities of how these inequalities influence childhood stunting are less well understood. Indeed, in some communities where short stature is common, there is controversy around whether childhood stunting should be considered a public health problem [7].

In this chapter, we have selected recently published papers from June 2021 to June 2022 on stunting and growth in childhood based on research on the antecedents, mechanisms,

and complex pathways underpinning childhood stunting. We also include recent data on nutrition-specific and nutrition-sensitive interventions including maternal health/well-being and women's economic empowerment. Finally, we have included publications that provide insights on how to improve governance, monitoring, and evaluation of nutrition interventions at the grassroots level and provide more robust and timely impact assessments.

Key articles reviewed for this chapter

Trends and Pathways

Epithelial abnormalities in the small intestine of Zambian children with stunting
Mulenga C, Sviben S, Chandwe K, Amadi B, Kayamba V, Fitzpatrick JAJ, Mudenda V, Kelly P
Front Med (Lausanne) 2022;9:849677

Site specific incidence rate of virulence-related genes of enteroaggregative *Escherichia coli* and association with enteric inflammation and growth in children
Das R, Palit P, Haque MA, Mahfuz M, Faruque ASG, Ahmed T
Sci Rep 2021;11:23178

Pathogens associated with linear growth faltering in children with diarrhea and impact of antibiotic treatment: the global enteric multicenter study
Nasrin D, Blackwelder WC, Sommerfelt H, Wu Y, Farag TH, Panchalingam S, Biswas K, Saha D, Jahangir Hossain M, Sow SO, Reiman RFB, Sur D, Faruque ASG, Zaidi AKM, Sanogo D, Tamboura B, Onwuchekwa U, Manna B, Ramamurthy T, Kanungo S, Omore R, Ochieng JB, Oundo JO, Das SK, Ahmed S, Qureshi S, Quadri F, Adegbola RA, Antonio M, Mandomando I, Nhampossa T, Bassat Q, Roose A, O'Reilly CE, Mintz ED, Ramakrishnan U, Powell H, Liang Y, Nataro JP, Levine MM, Kotloff KL
J Infect Dis 2021;224(12 Suppl 2):S848–S855

Child stunting starts in utero: growth trajectories and determinants in Ugandan infants
Namirembe G, Ghosh S, Ausman LM, Shrestha R, Zaharia S, Bashaasha B, Kabunga N, Agaba E, Mezzano J, Webb P
Matern Child Nutr 2022;18:e13359

The relationship between wasting and stunting in young children: a systematic review
Thurstans S, Sessions N, Dolan C, Sadler K, Cichon B, Isanaka S, Roberfroid D, Stobaugh H, Webb P, Khara T
Matern Child Nutr 2022;18:e13246

Consequences

Economic costs of childhood stunting to the private sector in low- and middle-income countries
Akseer N, Tasic H, Nnachebe Onah M, Wigle J, Rajakumar R, Sanchez-Hernandez D, Akuoku J, Black RE, Horta BL, Nwuneli N, Shine R, Wazny K, Japra N, Shekar M, Hoddinott J
eClinicalMedicine 2022;45:101320

Poor early childhood growth is associated with impaired lung function: evidence from a Ghanaian pregnancy cohort
Kaali S, Jack DW, Prah RKD, Chillrud SN, Mujtaba MN, Kinney PL, Tawiah T, Yang Q, Oppong FB, Gould CF, Osei M, Wylie BJ, Agyei O, Perzanowski MS, Asante KP, Lee AG
Pediatr Pulmonol 2022;57:2136–2146

Early childhood stunting and later life outcomes: a longitudinal analysis
Deshpande A, Ramachandran R
Econ Hum Biol 2022;44:101099

Interventions

Small-quantity lipid-based nutrient supplements for the prevention of child malnutrition and promotion of healthy development: overview of individual participant data meta-analysis and programmatic implications
Dewey KG, Stewart CP, Wessells KR, Prado EL, Arnold CD
Am J Clin Nutr 2021;114 (Suppl 1):3S–14S

A novel intervention combining supplementary food and infection control measures to improve birth outcomes in undernourished pregnant women in Sierra Leone: a randomized, controlled clinical effectiveness trial
Hendrixson DT, Smith K, Lasowski P, Callaghan-Gillespie M, Weber J, Papathakis P, Iversen PO, Koroma AS, Manary MJ
PLoS Med 2021;18:e1003618

Do tradeoffs among dimensions of women's empowerment and nutrition outcomes exist? Evidence from six countries in Africa and Asia
Quisumbing AR, Sproule K, Martinez EM, Malapit H
Food Policy 2021;100:102001

Perspectives and Policy

Effective nutrition governance is correlated with better nutrition outcomes in Nepal
Namirembe G, Shrestha R, Mezzano J, Ausman LM, Davis D, Baral K, Ghosh S, Shively G, Webb P
BMC Pediatrics 2021;21:434

Nutrition modeling tools: a qualitative study of influence on policy decision making and determining factors
Knight F, Bourassa MW, Ferguson E, Walls H, de Pee S, Vosti S, Martinez H, Levin C, Woldt M, Sethurman K, Bergeron G
Ann N Y Acad Sci 2022;1513:170–191

Revisiting the stunting metric for monitoring and evaluating nutrition policies
Subramanian SV, Karlsson O, Kim R
Lancet Glob Health 2022;10:e179–e180

Epithelial abnormalities in the small intestine of Zambian children with stunting

Mulenga C[1], Sviben S[2], Chandwe K[1], Amadi B[1], Kayamba V[1], Fitzpatrick JAJ[2,3,4], Mudenda V[5], Kelly P[1,6]

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Front Med (Lausanne) 2022;9:849677

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https://pubmed.ncbi.nlm.nih.gov/35372420/

Comments: Nutrition supplementation during pregnancy and childhood does not overcome childhood stunting in LMICs, possibly due to environmental enteropathy (EE). EE is a condition of the small intestine that involves loss of villus, reduced absorption, and intestinal inflammation. However, the role of the alteration in the composition and function of the microbiome in this enteropathy remains unclear. It is not clear how much of the dysfunction is attributable to the altered composition and function of the microbiome, but recent evidence that microbiota-directed complementary foods can improve growth suggests that it may make a substantial contribution. The authors had previously found that gut epithelial lesions were key drivers of small intestinal leakiness and microbial translocation among children with SAM [8]. In this study, Mulenga et al. aimed to assess the gut epithelial abnormalities among children with EE and stunting, nonresponsive to nutrition interventions, using confocal laser endomicroscopy, histology, and electron microscopy of the biopsies. Visual images showed leakage from circulation to the gut in 97% of the children. Histology consistently showed gut epithelial micro-erosions, cell-cell adhesion anomalies, and defects in secretory cells (Paneth cells and goblet cells), which may all contribute to impairment of the mucosal barrier function and microbial translocation. These were consistent with those identified in children with SAM.

Site specific incidence rate of virulence-related genes of enteroaggregative *Escherichia coli* and association with enteric inflammation and growth in children

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Comments: Environmental enteric dysfunction (EED) (also referred to as environmental enteropathy, EE) is endemic in LMICs and caused by early and lifelong exposure to environmental enteropathogens including bacteria, parasites, and viruses such as enteroaggregative *Escherichia coli* (EAEC). This study aimed to estimate the site-specific incidence rates of gene-carrying strains of EAEC and identify their risk factors and the possible associations between EAEC, EED score, and linear growth among 1,705 children aged <24 months enrolled in the MAL-ED birth cohort (South America, sub-Saharan Africa, and Asia). Gene-carrying strains of EAEC were detected by TaqMan Array Cards from stool samples. Infection with the *AggR* gene-carrying strain of EAEC was the commonest overall (43%). EAEC was strongly associated with poor child growth and development, and changes in intestinal inflammation. Low maternal education, lack of improved floor, and having domestic cattle were associated with EAEC infection. These findings provide the basis for potential vaccine development aimed at reducing the EAEC burden and therefore EED, with the potential to improve linear growth among children living in impoverished communities in LMICs.

Pathogens associated with linear growth faltering in children with diarrhea and impact of antibiotic treatment: the global enteric multicenter study

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Comments: The study uses data from global enteric multicenter prospective matched case-control study of children with moderate to severe diarrhea to quantify the association between childhood diarrhea and linear growth faltering in children aged <24 months at 7 sites in sub-Saharan Africa and South Asia. Previous studies have reported the association between diarrhea disease and linear growth. However, the impact of specific pathogens or recommended antibiotic treatment in this process remains unclear. Interestingly, among 8,077 children with moderate to severe diarrhea across the sites, stunting (defined as height-for-age z-scores [HAZ] < −1) increased from 59% at enrollment to 65% at follow-up ($p < 0.0001$). This study found that 4 pathogens (*Cryptosporidium*, typical enteropathogenic *E. coli*, untreated *Shigella*, and enterotoxigenic *E. coli* encoding heat-stable toxin) were associated with linear growth failure. Significant improvement in linear growth was observed among children positive for *Shigella* treated by the World Health Organization–recommended antibiotics. These findings highlight the importance of timely identification and targeted treatment of diarrhea-causing enteric pathogens among children aged <24 months as a key strategy to promoting linear growth in early childhood in LMICs.

Child stunting starts in utero: growth trajectories and determinants in Ugandan infants

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Comments: There are increasing data predominantly from observational studies showing that childhood stunting starts in utero, but they do not account for variation in linear growth between children and a particular age. Using data of 4,528 infants from a Ugandan birth cohort study, the study assessed the relationship between the different growth patterns at birth with pre- and postnatal factors. The researchers found that the stunting occurred before birth and followed 4 distinct growth patterns: chronically stunted, recovery, borderline stunted, and normal (not stunted). Wasting and underweight were observed in all groups and wasting gradually increased among

those who were already stunted. The authors argue that disaggregating children's growth potentials relative to the different risk within each group is key to the design of nutrition interventions. It will be useful to see whether these findings are replicated in other birth cohorts in LMICs.

The relationship between wasting and stunting in young children: a systematic review

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Matern Child Nutr 2022;18:e13246

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Comments: This was a systematic review looking at the relationship between wasting and stunting from studies conducted after 2014 among children under 5 years of age from LMICs. Forty-five studies were included in this review. The key findings were that the peak incidence of both wasting and stunting is between 0 and 3 months. There was also a strong association between the 2 conditions, whereby episodes of wasting lead to stunting, and to a lesser extent, stunting increases the risk of wasting. Children with concurrent stunting and wasting had a higher risk of mortality due to the impact of the dual burden on body composition and should therefore be appropriately risk stratified during treatment. The findings, therefore, challenge the existing status quo of having separate programs and strategies for the different but overlapping conditions. Instead, treatment strategies need to consider the risk of death as paramount to targeting interventions. In addition, while wasting and stunting are driven by common risk factors, targeting interventions by season and population characteristics (sex, and socioeconomic status) might be helpful to reduce the postnatal growth failure.

Economic costs of childhood stunting to the private sector in low- and middle-income countries

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Comments: Childhood stunting has economic consequences including reduced workforce productivity. Income losses of 5–7% in LMICs are associated with reduced workforce productivity as a result of stunting. These estimates reflect the national microeconomic estimates and do not include the private sector, which represents 90% of the workforce in LMICs. This study therefore aimed to quantify the economic burden and financial losses incurred by the private sector as a result of childhood stunting across 123 LMICs by using longitudinal datasets and national surveys. The findings showed that childhood stunting cost the private sector about USD 135.4 billion in sales annually representing 0.01–1.2% national GDP across these countries. Sectors most affected were food sectors, garments, and manufacturing. Monthly losses resulted in unearned losses ranging from USD 700 million to USD 16.5 billion, which could have been used by the stunted individuals to inject into their economies if stunting was eliminated in childhood. Estimates from the longitudinal studies showed that these stunted employees were not high-income earners; hence a slight increase in their earnings was associated with an increase in the access to essential resources. Reducing childhood stunting would therefore increase employees' human capital, and improve the employees' employment abilities and the national economy at large. Interestingly, women incurred a higher income penalty from childhood stunting and earned less than men; and the returns for investing in stunting reduction were consistently higher for men across most countries studied. These findings should motivate strong public-private sector partnerships to invest in childhood undernutrition, as this would address a myriad of socioeconomic challenges in LMICs including the gender disparities.

Poor early childhood growth is associated with impaired lung function: evidence from a Ghanaian pregnancy cohort

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Pediatr Pulmonol 2022;57:2136–2146

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Comments: Lung health in early childhood is a strong determinant of lung health over the life cycle. Impaired lung function as a result of undernutrition and poor growth is associated with an increased risk of childhood pneumonia and associated mortality. Despite this understanding, evidence on the modifiable risk factors of poor lung health in early childhood has remained scanty. Using the Ghana Randomized Air Pollution and Health Study (GRAPHS) [9, 10] cohort, the authors hypothesized that poor growth was associated with impaired lung function. The children had multiple anthropometric measurements (at birth and 3, 6, 9, 12 months and 4 years), and impulse oscillometry (lung function measurement) at 4 years. The study findings observed an inverse association between airway resistance with weight-for-age at birth ($\beta = -0.90$ cmH_2O/L/s, 95% CI: −1.64, −0.16) and HAZ at 4 years of age ($\beta = -0.40$ cmH_2O/L/s, 95% CI: −0.57, −0.22). Children with persistent stunting had a higher airway resistance compared to normal children in early childhood. This has adverse implications for their lung health in later childhood (increased risk of pneumonia) and adulthood.

Early childhood stunting and later life outcomes: a longitudinal analysis

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Econ Hum Biol 2022;44:101099

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Comments: This study used data of 6,357 children: 1,334 in Ethiopia, 1,690 in India, 1,609 in Peru and 1,724 in Vietnam to report on the long-term implications of childhood stunting. This showed that children who were severely stunted at 5 years had a 67% probability of being stunted at age 15; thus an indicator of future chronic malnutrition. The consequence for human capital is shown by the strong association with lower grade

completion by 22 years and the negative association with cognition in math, language, and reading scores at ages 8, 12, and 15 years and childhood stunting. They also found that access to skilled health personnel during pregnancy, as well as having at least 2 tetanus injections during pregnancy, was strongly associated with reduction in the incidence of stunting at 1 year. This suggests that provision of adequate and integrated maternal and child health services is a key to preventing childhood stunting.

Interventions

Small-quantity lipid-based nutrient supplements for the prevention of child malnutrition and promotion of healthy development: overview of individual participant data meta-analysis and programmatic implications

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Comments: While stunting often begins in utero, studies have reported a rapid decline in length-for-age between the 6–24-month period during complementary feeding. This meta-analysis reported the effects of providing lipid-based nutrient supplements to children aged 6–24 months. The prevalence of stunting, wasting, and underweight was 12–14% lower in children who received the small-quantity lipid-based nutrient supplement (SQ-LNS) compared to those who did not. Children who received SQ-LNS also had a 64% lower prevalence of iron-deficiency anemia compared with those in the control group. Gender, an effect modifier, showed stronger effects among girls than among boys, with SQ-LNS reducing the prevalence of stunting among girls by 16 versus 9% among boys. In girls, the overall mean for anthropometric *z*-scores was higher than in boys, suggesting that they may have a greater potential to respond rather than benefiting from the supplementation. The effect modification results emphasize that targeting during interventions for particular outcomes such as iron status, anemia, and child development should be considered on the basis of population-level socioeconomic status or burden of undernutrition, as some subgroups showed greater potential to benefit from the intervention. These interesting findings provide an opportunity for existing programs to incorporate the use of SQ-LNS in their interventions as a prevention of malnutrition strategy.

A novel intervention combining supplementary food and infection control measures to improve birth outcomes in undernourished pregnant women in Sierra Leone: a randomized, controlled clinical effectiveness trial

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Comments: The use of nutritional supplements in single or multiple formulation to treat undernutrition in pregnancy has yielded modest improvements. The observed modest effect of supplementation on linear growth in newborns suggests that dietary strategies alone are unlikely to reduce the risk of stunting in utero. This trial provided 1,489 undernourished pregnant women with ready-to-use supplementary food alongside azithromycin and testing and treatment for vaginal dysbiosis. The results showed that the recovery rate from undernutrition was 7.2% higher in women receiving the intervention than those receiving standard care (blended corn/soy flour and intermittent preventive treatment for malaria in pregnancy). Maternal weekly weight gain was greater in the intervention group (mean difference 40 g; 95% CI 9.70 to 71.0, $p = 0.010$) compared to those receiving standard care. However, maternal postpartum mid-upper arm circumference (MUAC) was not significantly different between the 2 intervention arms. Infants born to mothers in the intervention group were 0.3 cm longer and had MUACs that were 0.1 cm larger than infants born to mothers receiving the standard care. Fewer infant deaths were reported in the intervention group (35; 5.6%) than in the standard care group (53; 8.9%). A mortality benefit was observed in the intervention group within the first 21 days where 13 (1.9%) infants died compared to 28 (4.3%) in the standard care group. While the results of this study emphasize the importance of combining nutritious RUSF with infection prevention strategies during pregnancy, the widespread administration of azithromycin in pregnancy elicits important concerns of emergence of antibiotic-resistant strains. A dilemma presents itself as to the risks of widespread administration versus the chance to decrease neonatal death by 2.3-fold. Though the intervention is promising, further studies need to be carried out to understand the effects of routine prenatal azithromycin on maternal and infant carriage of resistant organisms.

Do tradeoffs among dimensions of women's empowerment and nutrition outcomes exist? Evidence from six countries in Africa and Asia

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Food Policy 2021;100:102001

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Comments: The study applied Women's Empowerment in Agriculture Index, an internationally validated measure based on interviews of women and men within the same household, from 6 countries to identify which indicators and dimensions of women's empowerment are related to dietary and nutrition outcomes in women and children. Results showed that the women's empowerment score was positively associated with improved child HAZ and better child nutrition. Higher HAZ was associated with women's empowerment domains where women made more agricultural decisions (p = 0.05), had a higher number of agriculture assets with rights (p = 0.05), made a higher number of credit decisions, and had greater satisfaction with leisure (p = 0.06). A decrease in intrahousehold inequality was associated with a higher likelihood of exclusive breastfeeding and higher HAZ. Women's empowerment had differential associations with boys' and girls' nutritional outcomes. In Bangladesh and Nepal, women's empowerment showed a negative association with girls' HAZ compared to boys' HAZ, while in Cambodia where a larger number of decisions are made by women, there were differential positive associations for girls' anthropometric outcomes compared to boys and the intrahousehold inequality was associated with higher HAZ and weight-for-age-z score (WAZ) for girls. Interestingly, not all empowerment domains were positively correlated with better nutrition. For instance, improved household dietary diversity required women to invest more time in agricultural activities, which results in increased energy expenditure, with consequences of lower maternal BMI and less time for childcare. These findings are important for nutrition-sensitive programs, emphasizing that empowering women and improving gender equality alone cannot address poor child nutrition. Addressing household wealth and country-level factors are also important.

Effective nutrition governance is correlated with better nutrition outcomes in Nepal

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BMC Pediatrics 2021;21:434

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Comments: There is a gap in understanding whether effective nutrition governance correlates with better anthropometric scores in children. This study therefore aimed to examine this association between effective nutrition governance by using the Nutrition Governance Index (NGI), derived from interviews with 520 government and nongovernment officials and anthropometry, utilizing data from 2 national studies in Nepal: the Policy and Science for Health, Agriculture and Nutrition (PoSHAN) community study and the PoSHAN policy. The study found that this relationship was positive for children over 2 years of age. A higher NGI was positively associated with HAZ and weight-for-height-z score (WHZ) for children >2 years, compared to younger children (HAZ: $\beta = 0.02$, $p < 0.004$, WHZ: $\beta = 0.01$, $p < 0.37$). A one-point increase in the NGI was significantly associated with a 12% increase in HAZ and a 4% increase in WHZ in older children aged > 24 months. The study findings highlight the crucial role of effective management of policy-based programming and resource in improving child nutrition and growth. Measuring NGI may be used as a tool to help governments monitor their progress in implementing child nutrition policies.

Nutrition modeling tools: a qualitative study of influence on policy decision making and determining factors

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Ann N Y Acad Sci 2022;1513:170–191
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Comments: While nutrition modeling tools (NMTs) have generated evidence needed for policy decisions and program implementation in LMICs, there is a gap on how the evidence they generate is applied and any influence it has had on policy or program decisions. In this study, 109 interviews were conducted with informants from 30 LMICs to explore how NMTs influence policy and factors that lead to this. Findings showed that NMTs were mostly applied by international organization to inform national government decision making. Equipping government officials and consumers to have a better understanding of the cycle of evidence generation, the application of evidence to inform policy and the implementation and uptake of policies for nutrition is vital. Creating an environment where stakeholders and government partners are more confident to interpret and present modeling data built a solid case for continued use of modeling locally and increased sense of ownership. Local leadership in evidence generation also helped put the local agenda on the forefront with limited influence of external agendas that would seek to overshadow national interests. There is need for further studies to understand how NMTs can be better applied in the future in terms of better planning for evidence generation, resources to support NMT application, modification, and new tool development as well as supporting local stakeholders' participation and local adaptation of evidence.

Revisiting the stunting metric for monitoring and evaluating nutrition policies

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Lancet Glob Health 2022;10:e179–e180
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Comments: The authors of this article question the accuracy of using stunting as a metric for measuring child undernutrition in India. They proceed to caution Indian policymakers regarding the use of stunting metrics to measure the effectiveness of interventions in the next phase of India's nutrition program PoSHAN Abhiyaan 2.0. Firstly, the mothers in the Indian Multicenter Growth Reference Study (MGRS) were much taller than the average population. The stunting metric incorporates intergenerational components of child growth, thus children born to short mothers determined by their own nutrition insults are more likely to pass that down to their offspring. Current policies being

implemented cannot thereby change the past nutrition and environmental insults that played a key role in determining maternal height. Secondly, they argue that calculating India's stunting prevalence using MGRS will, to an extent, result in an overestimation of child undernutrition. The MGRS focuses on the analysis of growth patterns of a specific population that is under an ideal environment and does not determine whether the pattern would be homogenous if compared to the children in poor environments at the same age at the same point in time. They continue to argue that adjusting for maternal height would not only grossly underestimate the effect of ongoing exposures to deficient conditions on a child's height but would also mean readjustment of multiple indicators of child growth and development that are determined by genetic and environmental factors. Changing how stunting prevalence is calculated for specific populations compared to the rest globally will not only cause confusion but would hamper global efforts to achieve sustainable development goals in relation to reduction of child undernutrition.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 32–46 (DOI: 10.1159/000527937)

The Physiology and Mechanisms of Growth

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Introduction

Further elucidation of the physiologic processes involved in growth has been made in the past year. Not surprisingly, the role of nutrition has been further confirmed as one of the most important factors in growth. A selection of the most important articles published in the period from July 1, 2021 to June 30, 2022 dealing with physiology and mechanisms of growth is presented in this chapter.

In this year's collection, several themes have been covered. Nutritional supplementation as a tool for optimizing growth has been further studied and could be used in everyday clinical practice in selected populations. Choosing the right protein and caloric value of the supplement, and also timing of the intervention, is paramount for the success. A link between nutritional state, puberty, and growth has been determined in MC3R, which is important not only for linear growth, but also for the management of chronic diseases and aging. Mechanisms behind the benefits of quality sleep in children for linear growth have been determined by studying the relationship between melatonin action and growth. Signaling processes involved in the regulation of endochondral ossification, as are matrix-bound extracellular vesicles, have been described. In addition, studies in the growth plate showed the importance of local glucose metabolism. More candidates for potential manipulation in relation to increased growth in idiopathic short stature (ISS) have been identified. There are additional data on the effectiveness of growth hormone (GH) therapy in certain innate diseases of the growth plate or induced by glucocorticosteroid treatment.

In the comments we try to explain why, in our opinion, these articles need to be especially highlighted. We, however, encourage the readers to read the full versions of the articles, when possible, and form their own opinions.

Key articles reviewed for this chapter

Different effects of soy and whey on linear bone growth and growth pattern in young male Sprague-Dawley rats
Bar-Maisels M, Menahem C, Gabet Y, Hiram-Bab S, Phillip M, Gat-Yablonski G
Front Nutr 2021;8:739607

Effect of a nutritional supplementation on growth and body composition in short and lean preadolescent boys: a randomised, double-blind, placebo-controlled study
Fisch Shvalb N, Lazar L, Demol S, Mouler M, Rachmiel M, Hershkovitz E, Shamir R, Phillip M, Yackobovitch-Gavan M
Acta Paediatr 2022;111:141–150

Associations of obesity with linear growth and puberty
Shalitin S, Gat-Yablonski G
Horm Res Paediatr 2022;95:120–136

MC3R links nutritional state to childhood growth and the timing of puberty
Lam BYH, Williamson A, Finer S, Day FR, Tadross JA, Gonçalves Soares A, Wade K, Sweeney P, Bedenbaugh MN, Porter DT, Melvin A, Ellacott KLJ, Lippert RN, Buller S, Rosmaninho-Salgado J, Dowsett GKC, Ridley KE, Xu Z, Cimino I, Rimmington D, Rainbow K, Duckett K, Holmqvist S, Khan A, Dai X, Bochukova EG, Genes & Health Research Team, Trembath RC, Martin HC, Coll AP, Rowitch DH, Wareham NJ, van Heel DA, Timpson N, Simerly RB, Ong KK, Cone RD, Langenberg C, Perry JRB, Yeo GS, O'Rahilly S
Nature 2021;599(7885):436–441

Deletion of Glut1 in early postnatal cartilage reprograms chondrocytes toward enhanced glutamine oxidation
Wang C, Ying J, Niu X, Li X, Patti GJ, Shen J, O'Keefe RJ
Bone Res 2021;9:38

Circadian rhythm modulates endochondral bone formation via MTR1/AMPKβ1/BMAL1 signaling axis
Yu S, Tang Q, Chen G, Lu X, Yin Y, Xie M, Long Y, Zheng W, Guo F, Shao L, Shi A, Chen L
Cell Death Differ 2022;29:874–887

Melatonin contributes to the hypertrophic differentiation of mesenchymal stem cell-derived chondrocytes via activation of the Wnt/β-catenin signalling pathway: melatonin promotes MSC-derived chondrocytes hypertrophy
Wang X, He T, He L, Yang B, Liu Z, Pang M, Xie P, Zhang L, Rong L
Stem Cell Res Ther 2021;12:467

LCN2 is a new diagnostic biomarker and potential therapeutic target in idiopathic short stature
Liu X, Zhang J, Yuan J, Ding R, Liu T, Jia J
J Cell Mol Med 2022;26:3568–3581

Treatment of short stature in aggrecan-deficient patients with recombinant human growth hormone: 1-year response
Muthuvel G, Dauber A, Alexandrou E, Tyzinski L, Andrew M, Hwa V, Backeljauw P
J Clin Endocrinol Metab 2022;107:e2103–e2109

Combined growth hormone and insulin-like growth factor-1 rescues growth retardation in glucocorticoid-treated mdxmice but does not prevent osteopenia
Wood CL, van 't Hof R, Dillon S, Straub V, Wong SC, Ahmed SF, Farquharson C
J Endocrinol 2022;253:63–74

The role of matrix-bound extracellular vesicles in the regulation of endochondral bone formation
Boyan BD, Asmussen NC, Lin Z, Schwartz Z
Cells 2022;11:1619

Effect of enteral zinc supplementation on growth and neurodevelopment of preterm infants: a systematic review and meta-analysis
Alshaikh B, Abo Zeed M, Yusuf K, Guin M, Fenton T
J Perinatol 2022;42:430–439

Growth hormone treatment in the pre-transplant period is associated with superior outcome after paediatric kidney transplantation
Jagodzinski C, Mueller S, Kluck R, Froede K, Pavičić L, Gellermann J, Mueller D, Querfeld U, Haffner D, Zivicnjak M
Paediatr Nephrol 2022;37:859–869

Effects of vitamin D and high dairy protein intake on bone mineralization and linear growth in 6- to 8-year-old children: the D-pro randomized trial
Stounbjerg NG, Thams L, Hansen M, Larnkjær A, Clerico JW, Cashman KD, Mølgaard C, Damsgaard CT
Am J Clin Nutr 2021;114:1971–1985

Dynamic changes in serum IGF-1 and growth during infancy: associations to body fat, target height and PAPPA2 genotype
Upners EN, Ljubicic ML, Busch AS, Fischer MB, Almstrup K, Petersen JH, Jensen RB, Hagen CP, Juul A
J Clin Endocrinol Metab 2022;107:219–229

The effects of nutrition on linear growth
Inzaghi E, Pampanini V, Deodati A, Cianfarani S
Nutrients 2022;14:1752

Different effects of soy and whey on linear bone growth and growth pattern in young male Sprague-Dawley rats

Bar-Maisels M[1,2], Menahem C[3], Gabet Y[3], Hiram-Bab S[3], Phillip M[1,2,3], Gat-Yablonski G[1,2,3]

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Front Nutr 2021;8:739607

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https://pubmed.ncbi.nlm.nih.gov/34901105/

Comments: Which kind of protein is better for supporting linear growth? Should we choose plant-based (soy) or animal-based (whey) protein for this purpose. In this elegant study, it has been determined that although in the short term soy leads to a faster growth and better bone quality, in the long term whey was associated with better linear growth outcomes and better bone mineralization. The authors discuss the mechanisms behind the observed findings, as are protein amino acid composition of the supplements, calcium absorption, effects on the insulin-like growth factor 1 (IGF-1) circulating levels, and effects on microbiota.

This study needs further validation in humans; however, it should be already considered in the planning of diets, especially in refeeding context. From the ecological point of view, the authors suggest that mixing plant-based and animal-based proteins in the human diet might be the most reasonable approach to a balanced and beneficial management plan. On the other hand, the timing of when soy- or whey-based products should be used is also important. Soy has a more rapid effect and whey has a more prolonged effect.

Effect of a nutritional supplementation on growth and body composition in short and lean preadolescent boys: a randomised, double-blind, placebo-controlled study

Fisch Shvalb N[1], Lazar L[1,2], Demol S[1], Mouler M[1], Rachmiel M[2,3], Hershkovitz E[4], Shamir R[2,5], Phillip M[1,2], Yackobovitch-Gavan M[1,2]

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Acta Paediatr 2022;111:141–150

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https://pubmed.ncbi.nlm.nih.gov/34346091/

Comments: During puberty, there is an increased demand of the body for energy and nutrients. The nutritional needs during puberty are gender specific, with increased demand in boys. Therefore, suboptimal nutrition during puberty could result in suboptimal

growth during this period, especially in boys who do not have sufficient energy intake. Effects of nutritional supplementation on growth were previously described [1, 2]. To this effect, an intervention with a specially designed formula was studied in a population of lean prepubertal boys in a double-blind randomized controlled study for 6 months. In comparison to the placebo, the formula had a higher caloric value and significantly increased levels of proteins, carbohydrates, and fat. In addition, it was fortified with calcium, iron, zinc, and vitamins A and C. Following the intervention, a significantly increased height was determined in boys receiving the formula. These data not only corroborate those related to the importance of nutrition in linear growth, but also suggest that they should be gender and pubertal stage specific. The described approach represents a new and validated management option in short and lean boys.

Associations of obesity with linear growth and puberty

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Horm Res Paediatr 2022;95:120–136
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https://pubmed.ncbi.nlm.nih.gov/34130293/

Comments: Under- and overnutrition have an important influence on growth pattern and final height. This review is a must-read compilation of up-to-date studies on the effects of overnutrition/obesity on linear growth in children. Authors describe mechanisms leading to the described observations, which are important for the reader's everyday clinical practice, when approaching children with obesity, as well as in planning preventive or curative measures for obesity. The authors emphasize the role of the adipose tissue, as an important endocrine organ in this respect. The role of leptin, possibly the main adipokine, is especially highlighted. Leptin affects linear growth by both directly acting at the growth plate and by regulating the GH-IGF-1 axis. In addition, the link between adipose tissue endocrine function and puberty start and progression and the effect this has on linear growth is discussed.

MC3R links nutritional state to childhood growth and the timing of puberty

Lam BYH[1,2], Williamson A[1,2,3], Finer S[4], Day FR[3], Tadross JA[1,2,5], Gonçalves Soares A[6], Wade K[6], Sweeney P[7], Bedenbaugh MN[8], Porter DT[7], Melvin A[1,2], Ellacott KLJ[9], Lippert RN[10], Buller S[1,2], Rosmaninho-Salgado J[11], Dowsett GKC[1,2], Ridley KE[12], Xu Z[12], Cimino I[1,2], Rimmington D[1,2], Rainbow K[1,2], Duckett K[1,2], Holmqvist S[12], Khan A[4], Dai X[13], Bochukova EG[13], Genes & Health Research Team, Trembath RC[14], Martin HC[15], Coll AP[1,2], Rowitch DH[12], Wareham NJ[3], van Heel DA[4,13], Timpson N[6], Simerly RB[8], Ong KK[3,12], Cone RD[7,16], Langenberg C[3,17], Perry JRB[3], Yeo GS[1,2], O'Rahilly S[1,2]

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Nature 2021;599(7885):436–441
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Comments: The leptin-melanocortin pathway is possibly the most important regulator of energy intake and energy expenditure. Mutations in this signaling pathway are associated with increased appetite, development of obesity, and also other clinical features. Medications targeting this pathway are being developed to mediate this dysregulation. MC3R, which is mainly expressed in the brain, is a part of this system. Its role in the development of obesity is discussed; however, as this important work suggests it seems to be an important link between the timing of puberty, pattern of linear growth, and body composition. Namely, loss-of-function in this receptor has been linked to delayed puberty and reduced linear growth in addition to reduced lean mass and circulating IGF-1 levels. These findings further identify the leptin-melanocortin pathway as an important regulator of puberty and growth and suggest that signaling through MC3R might be responsible for selectively regulating puberty and growth. In addition, selectively stimulating the MC3R might preferentially lead to the development of lean mass (and not fat mass), which is of importance in chronic diseases management and aging.

Deletion of Glut1 in early postnatal cartilage reprograms chondrocytes toward enhanced glutamine oxidation

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Bone Res 2021;9:38
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https://pubmed.ncbi.nlm.nih.gov/34426569/

Comments: It has been recently determined that glucose transporter 1 (GLUT1)-mediated glucose metabolism has an essential role in embryonic cartilage development and linear bone growth. Lack of GLUT1 was linked to decreased osteoblast differentiation and mineralization [3, 4].

GLUT1 seems to be the main glucose transporter in the cartilage. The role of glucose metabolism in postnatal cartilage growth was investigated in a mice model with selective early postnatal glucose transporter 1 (GLUT1) deletion in the chondrocytes. It was determined that GLUT1-mediated glucose metabolism is critical for postnatal growth plate development resulting in reduced linear bone growth. Mechanistically, it was linked to both by interfering with chondrocyte proliferation and matrix synthesis and processing. The results also show the metabolic plasticity of postnatal chondrocytes, since they are able to shift their metabolic pathways; in this case by using glutamine as an energy substrate, when glucose transport via GLUT1 was not possible. This shows the metabolic plasticity of the chondrocytes, which seems to be important when they are exposed to different metabolic demands during proliferation and differentiation and matrix synthesis and secretion.

In addition, the results of the study show different responses to GLUT1 silencing in different parts of the cartilage system. In articulate cartilage chondrocytes, postnatal GLUT1 deletion results in diminished cellularity and loss of proteoglycans, which ultimately progress to cartilage fibrosis. These changes lead to earlier osteoarthritis.

Altogether, this and related studies show the importance of glucose metabolism in growth plate chondrocytes both prenatally and in the early postnatal phase, the dysregulation leading to suboptimal growth.

Circadian rhythm modulates endochondral bone formation via MTR1/AMPKβ1/BMAL1 signaling axis

Yu S[1,2,3], Tang Q[1,2,3], Chen G[1,2,3], Lu X[1,2,3], Yin Y[1,2,3], Xie M[1,2,3], Long Y[1,2,3], Zheng W[1,2,3], Guo F[1,2,3], Shao L[4], Shi A[5], Chen L[1,2,3]

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Cell Death Differ 2022;29:874–887

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https://pubmed.ncbi.nlm.nih.gov/35094018/

Melatonin contributes to the hypertrophic differentiation of mesenchymal stem cell-derived chondrocytes via activation of the Wnt/β-catenin signalling pathway: melatonin promotes MSC-derived chondrocytes hypertrophy

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Stem Cell Res Ther 2021;12:467

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https://pubmed.ncbi.nlm.nih.gov/34419165/

Comments: In these 2 articles the role of circadian rhythms in endochondral ossification is described. Melatonin interacts with various types of stem cells and typically stimulates proliferation and transition to mature cell type. It has been shown that it has an especially important role in chondrogenesis and osteogenesis [5]. These 2 articles describe the mechanisms behind these observations. In the first article, it has been shown that melatonin mediates its action by periodically activating melatonin receptor 1, which then by downstream signaling pathways affects cell proliferation and matrix synthesis in the growth plate. In the second article, the direct role of melatonin in terminal differentiation of chondrocytes in endochondral ossification is described, by acting through the Wnt signaling pathway. These data further show the importance of central circadian rhythms in linear growth and identify novel pathways for possible manipulation in growth disorders.

LCN2 is a new diagnostic biomarker and potential therapeutic target in idiopathic short stature

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J Cell Mol Med 2022;26:3568–3581

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https://pubmed.ncbi.nlm.nih.gov/35610759/

Comments: In this interesting study, the authors have shown that serum LCN2 expression is upregulated in children with ISS. Serum LCN2 showed high sensitivity and specificity in discriminating children with ISS from GH deficiency, precocious puberty, and normal control individuals. LCN2 is an innate immune factor belonging to the lipocalin superfamily.

It has been previously reported that LCN2 was overexpressed in patients with lupus nephritis and in other autoimmune inflammatory diseases. In an interesting set of studies, they have shown that overexpression of LCN2 suppresses food intake, and

impairs chondrocytes proliferation and bone formation in the growth plate. The authors also showed in an animal study that bone growth impairment due to overexpression of LCN2 could be reversal when the overexpression stopped. Therefore, the authors concluded that LCN2 is a valid biomarker for ISS diagnosis and may be a potential target for ISS therapy.

These results are interesting and surprising. The diagnosis of ISS is made after all known causes of short stature are excluded in an intensive workup, which includes assessment of the GH-IGF-1 axis but also other known causes like celiac or other known inflammations like inflammatory bowel disease, by collecting detailed anamnestic story and laboratory workup including complete blood count, C-reactive protein, and blood chemical analysis. We have learned to believe that the diagnosis of ISS is a basket that includes different undiscovered causes of short stature. We know that children with ISS might belong to a family where both parents and siblings are short (familial short stature) or an isolated case of short child in the family. I find it difficult to believe that all or even most children with ISS have a common cause. Therefore, I agree with the bottom-line of the recommendation made by the authors: a prospective, randomized, controlled, multicenter trial should be conducted to support or refute their findings.

Treatment of short stature in aggrecan-deficient patients with recombinant human growth hormone: 1-year response

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J Clin Endocrinol Metab 2022;107:e2103–e2109

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https://pubmed.ncbi.nlm.nih.gov/34922359/

Comments: In this study, the authors demonstrated the results of 1 year of treatment of short stature in aggrecan-deficient patients. In 10 patients, the median height velocity increased from 5.2 cm/year before intervention to 8.3 cm/year after 1 year of GH treatment and increased the Height Standard Deviation Score (HtSDS) by +0.62. Interestingly, skeletal maturation did not advance inappropriately and no adverse events related to the therapy were observed.

I assume that for many years we were treating children with aggrecan deficiency thinking that we were treating children with ISS since the correct diagnosis was not identified. However, despite the fact that this study reports only 1 year of response to therapy of only 10 participants and with no control group, it is still an important description. More multicenter studies of that uncommon condition with appropriate comparative control for a longer duration are needed to sort out the full response to GH therapy in this group of short individuals.

Combined growth hormone and insulin-like growth factor-1 rescues growth retardation in glucocorticoid-treated mdxmice but does not prevent osteopenia

Wood CL[1,2], van 't Hof R[3], Dillon S[1], Straub V[4], Wong SC[5], Ahmed SF[5], Farquharson C[1]

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J Endocrinol 2022;253:63–74

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https://pubmed.ncbi.nlm.nih.gov/35191394/

Comments: Duchenne muscular dystrophy (DMD) affects 1 in 4,000 live male births and is caused by mutations in the DMD gene on the X chromosome. The loss of dystrophin protein results in progressive replacement of muscle fibers by fat and fibrous tissue. Glucocorticoids are currently the mainstay of treatment of DMD. In this study the authors aimed to determine whether the combined administration of recombinant human growth hormone (rhGH) and IGF-1 could rescue the glucocorticoid-induced skeletal impairment and growth retardation in a mice model of DMD (mdx mice). The authors report that the combination of GH and IGF-1 increased somatic growth but did not improve the negative effects of long-term glucocorticoid treatment on bone growth or cortical bone development in their mice model. The question of how to overcome the effect of glucocorticoids on linear growth is not just limited to children with DMD. Many children are exposed to long-term glucocorticoid treatment for a variety of diseases with a deleterious effect on their longitudinal growth and bone metabolism. The use of animal models is the right way to go in testing possible medication that can change the course of growth in children who are exposed to long-term use of steroids despite the fact that animal models are not exactly equal in their response to therapy to those of human beings. I agree with the authors that more convincing evidence is needed before a clinical study is designed.

The role of matrix-bound extracellular vesicles in the regulation of endochondral bone formation

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Cells 2022;11:1619

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Comments: In this review, the authors update the readers on new information that was achieved in recent years related to the matrix-bound extracellular vesicles (MVs) in the regulation of endochondral bone formation. MVs were already reported in the literature in the 1960s. They are extracellular organelles ranging from 50 to 150 nm in diameter and are anchored to the extracellular matrix of the growth plate via integrin binding to collagen. They traditionally were known as the site of initial mineralization. With the progress made in laboratory methods, more information emerged. It became clear that in addition to enzymes and minerals and regulatory glycoproteins, MVs also contain micro-RNAs. It was also found that MVs, which are produced by the chondrocytes of the growth plate, have a different content of proteins and micro-RNAs if they are derived from the resting cells or from more mature cells like the pre-hypertrophic zone or hypertrophic cells. It was suggested that MVs have a role in transferring information between the cells within the growth plate. So, while the full role of the MV was not yet elucidated, more information is available to date and expected to come in the near future with the advancements of the laboratory research tool.
This is a well-written review with beautiful figures which I recommend reading.

Effect of enteral zinc supplementation on growth and neurodevelopment of preterm infants: a systematic review and meta-analysis

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J Perinatol 2022;42:430–439
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Comments: Zinc, an important trace element in the human body, plays a critical role in linear growth during childhood via various mechanisms. Preterm infants, especially those who are very preterm, are at a high risk of zinc deficiency, as fetal zinc accretion occurs mostly after 24 weeks of gestation. Other factors include low body stores, renal and gastrointestinal losses, low zinc intake, and increased demands due to the relatively high growth rate in infancy. Zinc is also very important for protein synthesis. Recent nutritional approaches in very preterm infants include a high-energy and high-protein-based feeding regimen, which may necessitate greater amounts of zinc in the early days of a very preterm infant. Zinc deficiency in preterm infants is often subclinical but may be associated with growth, weight gain, and neurodevelopmental outcomes. The question on whether extra zinc supplementation can improve clinical outcome in preterm infants is unclear and current research has yielded conflicting results.
This is a systematic review and meta-analysis of randomized controlled trials of zinc supplementation in preterm infants, focusing on growth and neurodevelopmental outcomes. A total of 8 randomized controlled trials which included 742 preterm infants were reviewed. Seven of the studies reported growth parameters at 3–6 months corrected age; 1 study reported growth parameters just prior to discharge from the

hospital. Three trials reported neurodevelopmental outcomes, with 2 studies reporting outcomes at 6–12 months corrected age, and 1 trial reporting outcome in less than 3 months corrected age. Results showed that zinc supplementation was associated with +0.5 SD higher in weight *z*-score (95% CI: +0.23 to +0.76) and +1.12 SD higher in length *z*-score (95% CI: +0.63 to +1.61). On the other hand, neurodevelopmental outcomes yielded less conclusive results. Most studies used a parent-reported questionnaire rather than objective assessments. The review identified that motor development may be better with zinc supplementation in preterm infants but not overall neurodevelopment. This is the first systematic review and meta-analysis of this topic and has raised important questions. An issue that was noted is the lack of safety data in the trials included and the relatively small number of cases included. Larger trials should be conducted to ascertain the safety of zinc supplementation and also address important issues like regimen, dose of zinc used, and timing of introduction as part of nutritional therapy.

Growth hormone treatment in the pre-transplant period is associated with superior outcome after paediatric kidney transplantation

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Paediatr Nephrol 2022;37:859–869

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https://pubmed.ncbi.nlm.nih.gov/34542703/

Comments: Childhood chronic kidney disease is associated with poor growth leading to significant short stature, which is often disproportionate short stature with preferential involvement of the legs. Despite success with kidney transplantation, studies document that adult height is impaired in about 40% of children with stage 5 chronic kidney disease who had undergone kidney transplantation. The use of rhGH has been shown to improve linear growth in childhood chronic kidney disease stage 3–5, in conjunction with management of nutritional issues and metabolic abnormalities. Due to concerns about the safety profile, in particular, the risk of transplant rejection, rhGH is generally discontinued following kidney transplant. The role of treatment with rhGH prior to kidney transplant is still poorly understood.

The authors in this research performed a prospective observational study aiming to evaluate linear growth following kidney transplant, in particular, studying the role of treatment with rhGH before kidney transplant. From a total of 947 children who received a kidney transplant from May 1998 to January 2020, a total of 146 prepubertal children were included in this study – 52 children received rhGH prior to kidney transplant, and 94 did not receive rhGH prior to kidney transplant. Of the 94 children who did not receive rhGH before kidney transplant 17 were treated with rhGH posttransplant. Following 7 years after kidney transplant, the height *z*-score was significantly higher in the group that received rhGH pretransplant (−0.85 vs. −1.76). The group

that did not receive rhGH pretransplant was noted to have a faster decline in transplant function, lower hemoglobin, higher C-reactive protein, and higher steroid exposure. While the results of this study seem to demonstrate that rhGH therapy before transplant in children with chronic kidney disease is associated with improvement in height, further studies are needed to evaluate if this improvement in height is also related to disease-related factors. The role of rhGH in kidney-related factors, inflammation, anemia, and nutritional factors should also be investigated in future studies.

Effects of vitamin D and high dairy protein intake on bone mineralization and linear growth in 6- to 8-year-old children: the D-pro randomized trial

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Am J Clin Nutr 2021;114:1971–1985

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Comments: It is known that vitamin D and dairy protein may improve bone mass accrual during childhood but also have a role in improving linear growth. The global increase in vitamin D deficiency is well documented. Existing recommendations in Nordic countries and the USA suggest that supplementation with vitamin D of 10 µg/day and 15 µg/day is needed. However, a recent meta-analysis suggests that 20 µg/day may be needed to maintain 25 hydroxy-vitamin D levels of greater than 50 nmol/L. Other than vitamin D supplementation, milk and dairy proteins could also improve linear growth and bone mineralization.

This clinical trial aimed to evaluate the combined and separate effects of vitamin D supplementation and high-protein or normal-protein yogurt on linear growth and bone health during the winter months in 6- to 8-year-old healthy children. The primary outcome was DXA total body less head bone mineral density. Secondary outcome measures evaluated included other DXA parameters including at lumbar spine, height, and biomarkers of bone turnover and linear growth. Participants were randomized to 20 µg/day of vitamin D or placebo, and to substitute 260 g/day dairy with high-protein yogurt (10 g protein/100 g) or normal-protein yogurt (3.5 g/100 g). Vitamin D supplementation led to a greater increase in total body less head bone mineral content and lumbar spine bone mineral density. DXA bone parameters and bone biomarker of bone formation (osteocalcin) were lower in the high-protein groups compared with the normal-protein groups. In summary, this clinical trial showed that supplementation of 20 µg/day of vitamin D in healthy 6- to 8-year-olds improved bone mass in the whole body and lumbar spine and can be recommended. However, there is no evidence for the introduction of high protein on the clinical outcomes.

Dynamic changes in serum IGF-1 and growth during infancy: associations to body fat, target height and PAPPA2 genotype

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J Clin Endocrinol Metab 2022;107:219–229

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Comments: IGF-1 is an important mediator of linear growth throughout childhood. In the infancy phase of growth, it is believed that IGF-1 may play a relatively smaller role in linear growth, although to date there are limited studies. In addition, normative data on IGF-1 and IGF binding protein 3 (IGFBP-3) in infancy are lacking. Recently, cord blood concentrations of pregnancy plasma protein A2 (PAPPA2) were negatively associated with birth weight and birth length. Another recent study also identified an association between PAPPA2 and height in children. PAPPA2 cleaves IGF-1 from its binding proteins and thereby leads to a greater increase in bioactive IGF-1.

The investigators in this study aim to evaluate the determinants of change in weight and length during infancy and to evaluate the impact of factors like IGF-1 and PAPPA2 on weight gain and length gain. A total of 233 healthy children (114 girls) were included in this study. All had repeated blood sampling throughout the first year of life. IGF-1 decreased during the first year of life in both boys and girls, whereas IGFBP-3 remained stable. Both IGF-1 and IGFBP-3 were associated with weight gain but not increase in length. This association was only noted in girls when the group was separated. The PAPPA2 genotype did not have any influence on weight gain or length. This study, therefore, suggests that the role of systemic factors like IGF-1 and IGFBP-3 is on an increase in mass or parameters of body composition rather than on an increase in bone length. Further studies should evaluate the effect of nutrition in the relationship between systemic factors like IGF-1 and IGFBP-3 and weight gain in infancy. This study also provided useful information on normative data of IGF-1 and IGFBP-3 in infancy.

The effects of nutrition on linear growth

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Nutrients 2022;14:1752

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https://pubmed.ncbi.nlm.nih.gov/35565716/

Comments: This recent review summarizes information on systemic endocrine factors and nutritional factors that regulate linear growth during childhood. The role of key macronutrients and micronutrients is included, as are endocrine regulations like the GH/IGF-1 axis and insulin but also other factors like leptin and FGF21. A brief summary of clinically relevant states was included in the review, for example, anorexia nervosa and obesity. A multitude of chronic childhood conditions are also implicated and are areas of focus for clinical researchers in this field.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: March 22, 2023

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Obesity, Metabolic Syndrome, and Nutrition

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Introduction

The increasing number of young patients with obesity worldwide is a major challenge for health care systems in industrial and in low- and middle-income countries. Childhood obesity tracks into adolescence and adulthood and is strongly correlated with the risk of adult poor health. Obesity is associated with an increased individual risk for the development of cardiometabolic comorbidities, as well as a decrease in health-related quality of life.

A sedentary lifestyle and high-calorie diet combined with a genetic predisposition have been shown to be a key factor in developing obesity.

Recent data suggest that the early-life environment can have lasting effects on the physiology and metabolism of the fetus and is associated with the early metabolic programming of human health. Some studies reviewed in this chapter show that a number of in utero exposures such as maternal diet and maternal intake of nonnutritive sweeteners (NNS) during pregnancy are associated with the subsequent development of childhood obesity and metabolic risk of the offspring. A metabolic signature at birth may help elucidate the mechanisms involved in metabolic health later in life. One of the reviewed studies investigated metabolic changes in cord blood that may predict subsequent infant overweight and obesity.

Early-life nutrition also has a significant impact on lifelong health. One of the studies evaluated the impact of consumption of cow's milk fat during infancy and childhood and child adiposity. Its findings demonstrate that compared to children who consumed reduced fat

milk, children who consumed whole milk had lower odds of overweight and obesity. Another study revealed that higher fruit juice intake in infancy was associated with greater abdominal adiposity in mid-childhood and early adolescence.

School environments that support healthy food behaviors may positively influence childhood obesity. School free fruit and vegetable (FFV) policies are used to promote healthy dietary habits and tackle obesity; however, a recent reviewed study observed that the nationwide FFV policy did not have any notable beneficial effect on weight status.

Other studies included in this chapter evaluated the impact of the diet composition on adiposity, fat distribution, and cardiometabolic risk markers. Different nutrient intakes in childhood were differentially associated with adolescent body fat accumulation. Additionally, the impact of higher consumption of ultraprocessed foods (UPFs) during childhood on increased adiposity is presented. One study found that the replacement of dietary carbohydrates with fats had favorable effects on lipoprotein cholesterol concentrations in adolescents and adults when fats were consumed as monounsaturated or polyunsaturated fatty acids but not as saturated fatty acids. In adults, the benefits of a high adherence to the Mediterranean diet (MD) to prevent cardiovascular events are widely known. A current systematic review presented in the chapter assessed whether interaction effects occur between an obesity genetic risk score and the adherence to MD on adiposity and metabolic syndrome (MetS) also in the young ages.

Children with obesity are prone to develop obesity-related comorbidities. One of the main comorbidities is nonalcoholic fatty liver disease (NAFLD). Current data found that dietary sugar restriction reduces hepatic de novo lipogenesis (DNL) and fasting insulin, in addition to reductions in hepatic fat among adolescents with NAFLD.

An additional study evaluated the potential relationship between vitamin D and cardiometabolic risk among children, and reported that vitamin D supplementation had positive effects on high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol (TC), with several significant changes persisting during the postsupplementation period.

Finally, considering the deleterious consequences of obesity in childhood, public health interventions are urgently called to take nutritional measures with policies that encourage healthy eating among children.

In this chapter, we review a selection of 15 notable articles published between July 2021 and June 2022, focusing on the relation between nutrition, obesity, and metabolic comorbidities from infancy to childhood and young adulthood.

Key manuscripts reviewed for this chapter

Maternal Diet during Pregnancy and Risk of Childhood Obesity

Cord blood metabolic signatures predictive of childhood overweight and rapid growth
Handakas E, Keski-Rahkonen P, Chatzi L, Alfano R, Roumeliotaki T, Plusquin M, Maitre L, Richiardi L, Brescianini S, Scalbert A, Robinot N, Nawrot T, Sassi F, Vrijheid M, Vineis P, Robinson O
Int J Obes (Lond) 2021;45:2252–2260

Maternal diet quality during pregnancy is associated with biomarkers of metabolic risk among male offspring
Francis EC, Dabelea D, Shankar K, Perng W
Diabetologia 2021;64:2478–2490

Associations of maternal non-nutritive sweetener intake during pregnancy with offspring body mass index and body fat from birth to adolescence
Plows JF, Aris IM, Rifas-Shiman SL, Goran MI, Oken E
Int J Obes (Lond) 2022;46:186–193

Nutrition during Childhood and Risk of Childhood Obesity

Longitudinal associations of fruit juice intake in infancy with DXA-measured abdominal adiposity in mid-childhood and early adolescence
Wu AJ, Aris IM, Rifas-Shiman SL, Oken E, Taveras EM, Hivert MF
Am J Clin Nutr 2021;114:117–123

Cow's milk fat and child adiposity: a prospective cohort study
Vanderhout SM, Keown-Stoneman CDG, Birken CS, O'Connor DL, Thorpe KE, Maguire JL
Int J Obes (Lond) 2021;45:2623–2628

A nationwide school fruit and vegetable policy and childhood and adolescent overweight: a quasi-natural experimental study
Øvrebø B, Stea TH, Bergh IH, Bere E, Surén P, Magnus P, Juliusson PB, Wills AK
PLoS Med 2022;19(1):e1003881

Association between childhood consumption of ultraprocessed food and adiposity trajectories in the Avon Longitudinal Study of Parents and Children birth cohort
Chang K, Khandpur N, Neri D, Touvier M, Huybrechts I, Millett C, Vamos EP
JAMA Pediatr 2021;175:e211573

Eating contexts and their associations with sociodemographic factors in Brazilian adolescents (EVA-JF Study)
Neves FS, Fontes VS, Nogueira MC, Pereira PML de Faria ER, Netto MP, Oliveira RMS, Cândido APC
Public Health Nutr 2022:1–13

Vegetarian diet, growth, and nutrition in early childhood: a longitudinal cohort study
Elliott LJ, Keown-Stoneman CDG, Birken CS, Jenkins DJA, Borkhoff CM, Maguire JL; on behalf of the TARGet KIDS! COLLABORATION
Pediatrics 2022;149:e2021052598

Nutrition and Risk of Obesity-Related Comorbidities

Association between diet quality index and cardiometabolic risk factors in adolescents: Study of Cardiovascular Risks in Adolescents (ERICA)

Ritter JDA, Cureau FV, Ronca DB, Blume CA, Teló GH, Camey SA, de Carvalho KMB, Schaan BD

Nutrition 2021;90:111216

Dietary macronutrient composition in relation to circulating HDL and non-HDL cholesterol: a federated individual-level analysis of cross-sectional data from adolescents and adults in 8 European studies

Pinart M, Jeran S, Boeing H, Stelmach-Mardas M, Standl M, Schulz H, Harris C, von Berg A, Herberth G, Koletzko S, Linseisen J, Breuninger TA, Nöthlings U, Barbaresko J, Benda S, Lachat C, Yang C, Gasparini P, Robino A, Rojo-Martínez G, Castaño L, Guillaume M, Donneau AF, Hoge A, Gillain N, Avraam D, Burton PR, Bouwman J, Pischon T, Nimptsch K

J Nutr 2021;151:2317–2329

Dietary sugar restriction reduces hepatic de novo lipogenesis in adolescent boys with fatty liver disease

Cohen CC, Li KW, Alazraki AL, Beysen C, Carrier CA, Cleeton RL, Dandan M, Figueroa J, Knight-Scott J, Knott CJ, Newton KP, Nyangau EM, Sirlin CB, Ugalde-Nicalo PA, Welsh JA, Hellerstein MK, Schwimmer JB, Vos MB

J Clin Invest 2021;131:e150996

Childhood nutrient intakes are differentially associated with hepatic and abdominal fats in adolescence: the EPOCH study

Cohen CC, Perng W, Bekelman TA, Ringham BM, Scherzinger A, Shankar K, Dabelea D

Obesity (Silver Spring) 2022;30:460–471

Mediterranean diet and genetic determinants of obesity and metabolic syndrome in European children and adolescents

Seral-Cortes M, Larruy-García A, De Miguel-Etayo P, Labayen I, Moreno LA

Genes (Basel) 2022;13:420

Vitamin D supplementation and cardiometabolic risk factors among diverse school children: a randomized clinical trial

Sacheck JM, Huang Q, Van Rompay MI, Chomitz VR, Economos CD, Eliasziw M, Gordon CM, Goodman E

Am J Clin Nutr 2022;115:73–78

Cord blood metabolic signatures predictive of childhood overweight and rapid growth

Handakas E[1], Keski-Rahkonen P[2], Chatzi L[3], Alfano R[1,4], Roumeliotaki T[5], Plusquin M[4], Maitre L[6,7,8], Richiardi L[9], Brescianini S[10], Scalbert A[2], Robinot N[2], Nawrot T[4], Sassi F[11], Vrijheid M[6,7,8], Vineis P[1], Robinson O[1]

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Int J Obes (Lond) 2021;45:2252–2260

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https://pubmed.ncbi.nlm.nih.gov/34253844/

Comments: Childhood obesity is a condition which, throughout the past 100 years, has transformed from a sign of wealth and health to a disease that according to the WHO is "one of the most serious challenges of the 21st century" [1, 2]. Considering its complex and multiorgan health consequences, understanding in utero perturbations that lead to the development of obesity and obesity-related complications and identifying early predictive markers is of utmost importance.

In this perspective, new metabolomic analysis might offer relevant information on the profiling of circulating small molecules that might characterize a metabolic state able to predict infant growth and overweight and obesity. Interestingly, in this study authors attempted to characterize the cord blood metabolic signatures of rapid growth in infancy and overweight in early childhood in 4 European birth cohorts, using untargeted liquid chromatography–mass spectrometry (LCMS)-based metabolic profiling. Authors were able to show that cholestenone and branched-chain amino acid levels in cord blood are predictive of rapid growth and overweight/obesity, respectively, among healthy deliveries from 4 European populations.

In multivariate analysis, authors also showed that the addition of metabolites substantially improved prediction of both rapid growth and overweight compared with models using traditional risk factors alone. Thus, cholestenone and branched-chain amino acids resulted to be suggestive of a role of the gut microbiome and nutrient signaling, respectively, in child growth trajectories.

Early infancy represents a window of developmental plasticity during which environmental exposures can modulate the risk of chronic disease. Accelerated postnatal weight gain trajectories are associated with increased risk of diabetes, obesity, and cardiovascular diseases both in humans and mammalian models. These data have implications for public health, as the postnatal period offers a window during which optimizing nutrition and/or growth rates could reap lifelong benefits. Thus, identify-

ing early markers of rapid infancy weight gain, a potentially modifiable risk factor for obesity and type 2 diabetes, may eventually permit interventions targeting children at high risk for metabolic disease.

Metabolomic analysis allows comprehensive quantification of hundreds of nutrients, metabolic intermediates, and small molecules from biological samples and has proven a powerful tool for biomarker discovery. Thus, further studies evaluating the cord blood metabolic signatures related to obesity risk and its related complications are aimed in order to better tailor preventive strategies to contrast obesity epidemic since early childhood.

Maternal diet quality during pregnancy is associated with biomarkers of metabolic risk among male offspring

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Diabetologia 2021;64:2478–2490

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https://pubmed.ncbi.nlm.nih.gov/34370046/

Comments: A growing body of evidence indicates that prenatal exposures, such as maternal high-fat or high-sugar diets, can have obesogenic effects in the offspring [3, 4]. Therefore, there is an urgent need to identify modifiable risk factors in pregnancy that could inform public health interventions and reduce the burden of obesity.

The Healthy Eating Index-2010 (HEI) measures dietary patterns that are marked by higher consumption of vegetables, fruit, fish, and unsaturated fats, in conjunction with lower intakes of red and processed meat and saturated fats. This study aimed to examine the association of maternal diet quality in pregnancy, as indicated by the HEI, with offspring metabolic biomarkers and body composition at age 4–7 years. On average, women had an HEI score of 55.0 throughout pregnancy, and 43.0% had a score >57, a threshold associated with lower adiposity at birth in this cohort. Women with a score >57 consumed fewer carbohydrates, less total fat, and slightly less protein compared with women with a score ≤57. A higher HEI score was associated with higher education, lower prepregnancy body mass index (BMI), not smoking during pregnancy, and lower physical activity. This may indicate that women with a higher HEI score had in general better lifestyle behavior. Higher maternal diet quality during pregnancy was associated with a more favorable glucose-insulin homeostasis and lipid profile in male offspring, as indicated by lower concentrations of glucose, insulin and homeostatic model assessment of insulin resistance, and the ratio of fasting triacylglycerols: HDL cholesterol, even after accounting for potential confounders and mediators. However, following further adjustment for the child's HEI score and physical activity levels, the magnitudes of associations for glucose and triacylglycerols:HDL were slightly attenuated and no longer reached the threshold of statistical signifi-

cance. This observation may point to the significance of healthy lifestyle also in early childhood to modify cardiometabolic risk biomarkers.

Interestingly, among girls, maternal HEI score was not associated with metabolic biomarkers or body composition after accounting for maternal and perinatal characteristics. This remarkable observation of sex dimorphism of maternal diet effect on metabolic biomarkers of the offspring may be explained by studies of the epigenome and transcriptome of murine and human placentas that have shown sex-specific differences in gene expression with respect to maternal diet during pregnancy [5, 6].

The study strength includes the relatively large number of included mother-offspring pairs with the long-term evaluation. The main limitation of the study is that the calculation of the HEI was based on data from dietary recalls collected over the course of pregnancy, which may suffer from recall bias.

Nevertheless, the onset of childhood obesity and associated metabolic traits that occur at early ages highlights the gestational period as a critical window during which prevention efforts could have long-lasting impacts.

Associations of maternal non-nutritive sweetener intake during pregnancy with offspring body mass index and body fat from birth to adolescence

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Int J Obes (Lond) 2022;46:186–193

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https://pubmed.ncbi.nlm.nih.gov/34611285/

Comments: Nonnutritive sweeteners (NNS) are widely consumed as "healthier" alternatives to sugar. Yet, recent evidence suggests NNS may adversely influence weight gain and metabolic health. The impact of NNS during critical periods of early development has rarely been studied. A recent study had shown, by triangulating evidence from humans, mice, and cultured adipocytes, that maternal NNS consumption during pregnancy may program obesity risk in offspring through effects on adiposity and adipocyte differentiation [7].

The purpose of the reviewed study was to examine the extent to which NNS intake during pregnancy is associated with offspring BMI *z*-score trajectory and body fat measures from birth to 18 years, using mother-child pairs. The findings of the study show that mothers who had the highest quartile of NNS intake versus the lowest quartile (Q4 vs. Q1) had higher prepregnancy BMI and were more likely to be of White ethnicity and smoke during pregnancy, which may point to less healthy lifestyle behaviors in general. In unadjusted and adjusted multivariable regression models, NNS intake in the highest versus lowest quartiles was associated with higher BMI *z*-score at infancy, early childhood, mid-childhood, and early adolescence, but not birth. High maternal NNS intake was also associated with higher sum of skinfolds in early childhood, mid-childhood, and early adolescence compared with low maternal NNS intake. In adjusted mixed-effect models, there was a positive interaction between the maternal NNS intake – offspring BMI *z*-score relationship and child age, which means

that the strength of the association between maternal NNS intake and offspring BMI *z*-score increased as the children aged.

The strengths of the study are the relatively large sample size, the detailed information collected (including covariates), and the longitudinal design as the researchers examined childhood BMI *z*-score longitudinally, from birth to age 18 years, and the use of 2 different measurements of body fat (sum of skinfolds and fat mass index).

The limitation of the study is that, since most of the participants were college educated and of White ethnicity, it limits the generalizability of the results. Also, the researchers did not include postexposure factors such as child dietary habits or physical activity, which could potentially modify relationships between maternal NNS consumption and childhood growth and adiposity. Moreover, these results are observational, and therefore conclusions about causality cannot be drawn.

Nutrition during Childhood and Risk of Childhood Obesity

Longitudinal associations of fruit juice intake in infancy with DXA-measured abdominal adiposity in mid-childhood and early adolescence

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Am J Clin Nutr 2021;114:117–123

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https://pubmed.ncbi.nlm.nih.gov/33829237/

Comments: Early introduction of complementary foods, sugar-sweetened beverages, and unsweetened fruit juice has been directly associated with obesity in young children [8]. The American Academy of Pediatrics recommends breast milk to be the sole source of nutrients during the infant's first 6 months of life and that solid foods or liquids be introduced around 6 months of age [9]. The American Academy of Pediatrics also recommends avoiding fruit juice and sugar-sweetened beverages during the infant's first year [9] because they have a high sugar content, lower nutrient content, and links with obesity and particularly with abdominal obesity.

Excessive adiposity and particularly abdominal adiposity is an independent risk factor for impaired glucose metabolism and to adverse cardiometabolic health in children [10]. Understanding the early-life factors influencing these abdominal adiposity measures is therefore important with the aim to develop strategies to prevent excessive abdominal adiposity and its associated cardiometabolic disease risk.

In this study, by using data from Project Viva, a longitudinal Boston area prebirth cohort, authors attempted to examine the associations of exposure to fruit juice intake in infancy with repeated measures of abdominal adiposity assessed by dual-energy X-ray absorptiometry in mid-childhood and early adolescence. Particularly, authors showed that higher fruit juice intake at age 1 year was associated with persistently greater visceral adipose tissue, subcutaneous abdominal adipose tissue, and total abdominal adipose tissue area standard deviation scores in mid-childhood and early

adolescence. These associations were observed to be greater in magnitude for visceral adipose tissue than for subcutaneous abdominal adipose tissue and total abdominal adipose tissue. Thus, these results suggest that exposure to higher fruit juice intake in infancy is associated with persistently greater abdominal adiposity, particularly visceral adiposity, in mid-childhood and early adolescence.

These findings reinforce the recommendations of limiting infant intake of fruit juice, which could have later impact on visceral adiposity in childhood and adolescence. In addition, these results support the implementation of early-life behavioral interventions to counter obesogenic feeding practices during infancy, particularly in those populations at higher risk of obesity and diabetes.

Cow's milk fat and child adiposity: a prospective cohort study

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Int J Obes (Lond) 2021;45:2623–2628

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https://pubmed.ncbi.nlm.nih.gov/34433906/

This article is also reviewed in the chapter by Larnkjær et al. [this vol., pp. 140–155].

Comments: International guidelines recommend that children aged 9 months to 2 years consume whole (3.25%) fat cow's milk, and children older than age 2 years consume reduced (0.1–2%) fat cow's milk to prevent obesity [11–13].

Previous systematic reviews already revealed that whole milk was associated with lower risk of childhood overweight or obesity among children aged 9 months to 18 years [14]. A recent study from USA estimated the associations of the frequency and fat content of early childhood milk intake with early adolescent adiposity and cardiometabolic risk [15]. Its finding showed that consumption of higher-fat cow's milk in early childhood was not associated with increased adiposity or adverse cardiometabolic health over a decade later.

The current study evaluated the longitudinal relationship between cow's milk fat (0.1–3.25%) intake and BMI z-score in childhood. On average, children who consumed whole milk had a 0.1 lower BMI z-score than children who consumed reduced fat milk. The researchers found that compared to children who consumed reduced fat (0.1–2%) milk, there was evidence that children who consumed whole milk had 16% lower odds of overweight and 18% lower odds of obesity.

Possible mechanisms underlying the observed relationship include that children who consume higher cow's milk fat may be more satiated than those who consume reduced fat cow's milk, leading them to consume a lower quantity of cow's milk or other energy-dense foods contributing to higher energy intake. Hormones secreted in response to whole milk consumption such as cholecystokinin and glucagon-like peptide 1 may play a role. Cow's milk fat contains unique fatty acids such as *trans-*

palmitoleic acid and conjugated linoleic acid, which may provide cardiometabolic benefits relative to other fatty acids. Therefore, cow's milk fat may not contribute to energy storage and adipose tissue as significantly as other types of dietary fat. Also, a lower-fat diet in early life may program the body to favor energy storage over utilization, which may increase the risk of obesity over the life course.

The strengths of the current study are its design to overcome weaknesses of previous analyses and minimize risk of bias through a large prospective cohort study with adjustment for important potentially confounding factors.

Its limitation includes that since the study participants were from healthy urban Canadian children, they may not be representative of other groups of children. Also, cow's milk with different fat contents may have been offered to children based on parent perception of body size.

The study findings support the guideline for children aged 9 months to 2 years, but suggest that guidelines for older children may not be effective in preventing childhood overweight or obesity and adverse cardiometabolic outcomes.

A nationwide school fruit and vegetable policy and childhood and adolescent overweight: a quasi-natural experimental study

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PLoS Med 2022;19(1):e1003881

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https://pubmed.ncbi.nlm.nih.gov/35041660/

Comments: Although, the global trends of rising BMI among children and adolescents have leveled off in many high-income countries, a shift toward an increased prevalence of severe form of obesity has been documented in males and females in all age groups [16]. Therefore, a stronger and negative effect of overweight and obesity during childhood on psychosocial and cardiovascular health as well as on its related increased morbidity and mortality that urgently need to be contrasted is expected. However, to date most of the adopted strategies have failed to reach their goals in contrasting the rise of the prevalence of obesity worldwide. Thus, effective prevention strategies are needed.

Unhealthy dietary behaviors such as skipping breakfast, irregular eating patterns, and the consumption of fast food and high-sugar beverages are known to contribute to obesity and are prevalent in this group of subjects. Evidence also suggests that young

people from areas of socioeconomic deprivation are less likely to consume fruit and vegetables and more likely to consume energy-dense fast foods. Understanding the social and environmental influences of eating behaviors has the potential to enhance the understanding of how to improve health outcomes for young people.

In this study, authors were able to explore the effect of a nationwide program adopted in Norway. Particularly, between 2007 and 2014, schools were obligated to provide a daily piece of free fruit or vegetable to all Norwegian children in combined schools (covering grades 1–10, age 6–16 years). Interestingly, using data from 11,215 Norwegian children and early adolescents, authors have observed little evidence of any beneficial or unintended impact from exposure to the FFV policy on weight outcomes in either boys or girls at age 8.5 and 13 years. Although authors were not able to show a strong impact of the Norwegian nationwide program on prevention of obesity, these results clearly show the need of population-wide approaches and particularly combined with physical activity. These programs need to be concentrated further at school level. In fact, schools are an optimal setting for health promotion due to the potential to reach all children regardless of sociodemographics.

Meta-analyses and systematic reviews [17] of randomized controlled trials indicate that increased fruit and vegetable consumption may promote weight loss and fruit and vegetables consumed may substitute for more energy-dense foods thus preventing weight gain. Information about the possible benefits or unintended consequences of school dietary interventions is clearly important. Despite this, there are very few evaluations of school fruit and vegetable provision. Therefore, further studies are needed in order to better tailor an effective school-based strategy with the aim to contrast the alarming increase of obesity and its related complication in childhood.

Association between childhood consumption of ultraprocessed food and adiposity trajectories in the Avon Longitudinal Study of Parents and Children birth cohort

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JAMA Pediatr 2021;175:e211573

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Comments: Ultraprocessed foods (UPFs) are industrial formulations of ingredients that undergo a series of physical, chemical, and biological processes. They typically lack intact healthy food components, include various additives, and tend to be more energy-dense and nutritionally poorer compared with less processed alternatives. Children are the leading consumers of UPFs.

A previous systematic review showed that most studies have found positive associations between consumption of UPF and increased body fat during childhood and adolescence [18]. A more recent systematic review that included 10 studies, 5 longitudinal and 5 cross-sectional, mainly conducted in Brazil, found that in 4 longitudinal studies in children with a follow-up longer than 4 years, there was a positive association between the consumption of UPF and obesity and adiposity parameters, whereas cross-sectional studies failed to find an association [19].

The current study assessed longitudinally the associations between UPF consumption and adiposity trajectories from childhood to early adulthood in a large cohort of British children. They found that children with higher UPF consumption were more likely to have lower maternal socioeconomic profiles compared with those in lower UPF quintiles. Their findings demonstrate that among those in the highest quintile of UPF consumption compared with their lowest quintile counterpart, trajectories of BMI increased by an additional 0.06/year; fat mass index by an additional 0.03/year; weight by an additional 0.20 kg/year; and waist circumference by an additional 0.17 cm/year.

The strengths of the study are the large sample size, the longitudinal long-term follow-up with a median of 10.2 years with an annual evaluation, the assessment of UPF consumption by detailed 3-day food diaries, and multiple adiposity measurements with assessment of the body fat mass by dual-energy X-ray absorptiometry measurements.

In addition, the advantage of the models they used is the inclusion of different covariates that may impact body weight such as birth weight, physical activity evaluated by accelerometer data, mean daily calorie intake, and maternal-related data (prepregnancy BMI, marital status, educational and socioeconomic status).

The findings of this cohort study suggest that higher consumption of UPFs in childhood is associated with more rapid progression of increased BMI and fat mass into adolescence and early adulthood. Since those from the lower socioeconomic status were the main consumers of UPFs, it calls for more effective public health actions that can reduce children's exposure and consumption of UPFs, maybe by lowering the prices of less processed alternatives and increased taxes on the food industry that promote these UPFs.

Eating contexts and their associations with sociodemographic factors in Brazilian adolescents (EVA-JF Study)

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Public Health Nutr 2022:1–13

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Comments: The rising incidence of metabolic diseases, namely, obesity, MetS, or type 2 diabetes mellitus, is one of the main social challenges ahead now and in the coming years. These diseases are closely related to dietary habits which need to be evaluated in the clinical setting of all outpatient pediatric obesity clinic. Diet surveys have been continuously demonstrating negative changes in the eating habits of adolescents, with reduced consumption of fruits and vegetables, increased consumption of soft drinks and other sugary drinks, and replacement of traditional culinary preparations, based on unprocessed or minimally processed foods, by UPFs. However, eating habits also include some peculiar aspects such as eating contexts (e.g., skipping breakfast, eating out, eating in front of screens, watching TV, playing videogames, or using smartphone/tablet/computer) or while studying and having meals without company which have been shown to be associated with a lower diet quality, lower daily ingestion of vitamins and minerals, and a greater BMI.

Therefore, the aim of this exploratory study was to estimate associations of eating contexts with food consumption according to the degree of industrial processing and overweight indicators in a relatively large sample of Brazilian adolescents. Particularly, authors were able to show that inappropriate eating contexts at breakfast and dinner were associated with a lower consumption of unprocessed or minimally processed foods and culinary ingredients, a higher consumption of UPFs, greater BMI-for-age, and greater percentage of body fat in Brazilian adolescents. Therefore, results of this study are relevant in order to provide information to design actions and nutrition programs applicable to the school environment, to improve food practices, prevent overweight, and promote an improvement in the health of the young population, since many lifestyle behaviors and risk factors tend to continue into adulthood.

Vegetarian diet, growth, and nutrition in early childhood: a longitudinal cohort study

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Pediatrics 2022;149:e2021052598

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Comments: Vegetarian and vegan diets become more popular also among children in recent years. However, these diets may have the risk of nutrient insufficiency without appropriate clinical follow-up and supplement use. On the other side, interventional trials

have consistently demonstrated that consumption of plant-based diets reduces body fat in overweight and obese subjects, even when controlling for energy intake. The major dietary mechanisms that may lead to reduced body fat include reduced caloric density, improved gut microbiota symbiosis, increased insulin sensitivity, reduced trimethylamine-N-oxide, activation of peroxisome proliferator-activated receptors, and overexpression of mitochondrial uncoupling proteins. Collectively, these factors improve satiety and increase energy expenditure leading to reduced body weight [20].

The aim of the current study was to examine the relationships between vegetarian diet and growth, micronutrient stores, and serum lipids among healthy children.

A higher percentage of children with vegetarian diet were more likely to have Asian ethnicity (33.8 vs. 19.0%), and a higher percentage of them got iron supplementation and vitamin D supplementation compared to nonvegetarian (10.6 vs. 5.6% and 49.6 vs. 41.9%, respectively), which may affect the results of the association between vegetarian diet and micronutrients.

The researchers did not find evidence of differences in mean BMI z-score or BMI z-score growth rates between children with vegetarian diet and nonvegetarian diet. They found that vegetarian diet was associated with higher odds of underweight, but there was no evidence of an association with overweight or obesity. They found a weak association between vegetarian diet and lower mean height z-score. No associations were found between vegetarian diet and serum ferritin, vitamin D, or serum lipids. Children with vegetarian diet who consumed little to no cow's milk had lower serum lipids than children with nonvegetarian diet. It may be assumed that children with vegetarian diet who do not consume cow's milk may drink a larger volume of plant-based milks, which have been identified to have a lipid-lowering effect in adults. However, children with and without vegetarian diet who consumed the recommended 2 cups of cow's milk per day had similar serum lipids.

The strengths of the study are the large sample size, the longitudinal design of the study, availability of anthropometric measures that were obtained by trained research assistants during each visit, and the inclusion in the analysis of potential confounders that were collected at each health care visit, along with exposure and outcome measures. The limitations of the study include the absence of detailed measures of dietary intake and physical activity and information on parental dietary intake which may impact body weight; also, the relatively short time follow-up duration of an average 2.8 years. Therefore, larger longitudinal cohort studies are required to allow the evaluation of the different types of vegetarian diet on longer-term outcomes.

Association between diet quality index and cardiometabolic risk factors in adolescents: Study of Cardiovascular Risks in Adolescents (ERICA)

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Nutrition 2021;90:111216

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Comments: Diet-related cardiometabolic diseases, such as obesity, diabetes, and cardiovascular disease, inflict considerable implications on our health and economy, also in childhood. Using dietary patterns to assess the association between diet and health outcomes has been suggested to be a potential tool to be integrated to the traditional single-nutrient approach [21, 22]. The main advantages of these indices are the possibility to assess the complexity of the human diet and summarize it into a score, taking into account dietary patterns, guidelines for a healthy diet, and food preparation methods. A dietary pattern summary score can be used to evaluate a subject's overall diet and categorize their intake based on the degree of adherence to the eating recommendations used to construct the score. This multidimensional approach allows us to detect the collective impact of multiple nutrients and delivering practical, holistic dietary messages, consistent with public health recommendations. However, most dietary indices were developed based on nutritional recommendations for adult populations and, consequently, are improper to accurately assess diet quality in adolescents.

Current evidence about the associations between each of these diet quality scores and cardiometabolic risk in pediatric populations is inconsistent, underscoring the need for prospective cohort studies that investigate the relationship between diet quality and cardiometabolic risk factor. In this study, by using the Diet Quality Index for Adolescents, which was designed and validated in a sample of adolescents enrolled in the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA), authors were able to explore the relationship between diet quality and cardiometabolic markers in a nationally representative sample Brazilian adolescents. Particularly, they showed that in normal-weight girls, higher scores were associated with better cardiometabolic profiles; however, no association was observed in those with overweight/obesity. In boys, a better quality of diet was associated with lower concentrations of LDL cholesterol, independent of the weight status, and with TC only in those with overweight/obesity. Thus, the evaluated score might be a helpful tool characterizing the association between diet quality and cardiometabolic markers in adolescents with the aim to modify some cardiometabolic risk factors present in childhood and

adolescence that are known to persist into adulthood, increasing the risk for premature development of cardiovascular disease and type 2 diabetes.
Further studies evaluating ethnic and regional differences in these and other available scores might offer more validation tools in childhood adoptable in the clinical setting.

Dietary macronutrient composition in relation to circulating HDL and non-HDL cholesterol: a federated individual-level analysis of cross-sectional data from adolescents and adults in 8 European studies

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J Nutr 2021;151:2317–2329
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Comments: Cardiovascular diseases represent the most common cause of death worldwide with clear evidences of the development of precocious alterations already since childhood. Although different factors including obesity, chronic inflammation, cytokine, and chronic disease might negatively affect cardiovascular risk, alterations in the lipoprotein metabolism such as high concentrations of TC and LDL cholesterol and low concentrations of HDL cholesterol certainly represent the key risk factors accounting for ~50% of cardiovascular diseases.

LDL cholesterol, intermediate-density lipoproteins, very low-density lipoproteins, and remnant lipoproteins represent the non-HDL cholesterol components of atherogenic particles. Interestingly, dietetic approaches aimed to affect the composition of the macronutrient have shown to modify these atherogenic particles, thus affecting the cardiovascular risk. Recent data have shown that non-HDL cholesterol correlated more closely with cardiovascular risk than LDL cholesterol, and non-HDL cholesterol has therefore recently emerged as a new target for the prevention of cardiovascular events [23]. Therefore, comprehensive studies evaluating the effects of diet on atherogenic molecules are needed in order to characterize the cardiovascular risk related to HDL and non-HDL cholesterol.

Thus, in this study authors investigated the association of the isocaloric replacement of carbohydrates with total fat or different types of fat with blood lipoproteins HDL cholesterol, non-HDL cholesterol, and the ratio of HDL cholesterol to TC (HDL cholesterol/TC) by sex and age in 8 European observational studies participating in the European Nutritional Phenotype Assessment and Data Sharing Initiative (ENPADASI) project. Interestingly, authors were able to show that the isocaloric replacement of carbohydrates with total fats or monounsaturated fatty acids was positively associated with HDL cholesterol, whereas the replacement of carbohydrates with saturated fatty acids was positively associated with non-HDL cholesterol concentrations. The replacement of carbohydrates with polyunsaturated fatty acids was inversely associated with non-HDL cholesterol concentrations.

Taken together these data confirm that the consumption of fats in place of carbohydrates have beneficial effects when fats are consumed in the form of monounsaturated fatty acids or polyunsaturated fatty acids but not saturated fatty acids. Thus, tailored dietetic approaches might strongly affect cardiovascular risk by modifying particularly those cholesterol-related atherogenic molecules. In addition, further studies confirming these data and particularly evaluating in a longitudinal setting early atherosclerotic marker [24] might fully elucidate the cause-effect relationship of such approaches aimed to reduce the cardiovascular risk already since childhood.

Dietary sugar restriction reduces hepatic de novo lipogenesis in adolescent boys with fatty liver disease

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J Clin Invest 2021;131:e150996

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Comments: NAFLD represents the most common chronic liver disease in childhood. In addition, it is considered the hepatic manifestation of MetS, thus representing a key alteration of a relevant condition which is well known to be strongly related to an increased risk of cardiovascular disease [25, 26].

Treatment and prevention of NAFLD are based on lifestyle intervention, thus representing diet the key point for its improvement. However, some nutrients could play a role in its pathophysiology. Particularly, experimental studies in adults have shown that shifting to high-sugar diets, especially diets containing fructose, increases both hepatic DNL and hepatic fat, even in the absence of weight gain [27]. While adult data are more robust, reports in children are limited.

In this study, authors were able to test the effect of 8 weeks of dietary sugar restriction on hepatic DNL in adolescent boys with NAFLD (11–16 years old) who participated in a randomized, controlled treatment study comparing a diet low in free sugars versus their usual diet. Hepatic DNL was measured as percentage contribution to plasma triglyceride palmitate using a 7-day metabolic labeling protocol with heavy water. Hepatic fat was measured by magnetic resonance imaging–proton density fat fraction. Interestingly, authors showed that treatment in adolescent boys with NAFLD decreased DNL by nearly one third (from 34.6 to 24.1%). Interestingly, these effects were shown to be independent of weight loss. In fact, this finding was similar, but slightly attenuated after adjusting for weight change during the intervention. In addition, authors showed that change in DNL was directly correlated with changes in free-sugar intake, fasting insulin, and alanine transaminase during the intervention. Overall, these findings are consistent with the hypothesis that dietary free-sugar restriction is a strategy for reducing hepatic DNL, which in turn is beneficial for other metabolic outcomes in pediatric NAFLD. Therefore, this study clearly confirmed the tight correlation between intake of sugar in the diet and NAFLD and particularly its ability to affect NAFLD by modulating DNL in children. Thus, due to the role of some nutrients in the pathophysiology of NAFLD, the complete knowledge of other major components is needed in order to better activate effective preventive and treatment strategies in children and adolescent at risk for or with NAFLD.

Childhood nutrient intakes are differentially associated with hepatic and abdominal fats in adolescence: the EPOCH study

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Obesity (Silver Spring) 2022;30:460–471

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https://pubmed.ncbi.nlm.nih.gov/35088559/

Comments: Studies have shown that greater abdominal fat deposition, especially visceral fat, and hepatic fat deposition are strong risk factors for insulin resistance and other cardiometabolic risk factors in youth, independent of total adiposity [28, 29].

It is known that obesity, nutrition, lifestyle variables, genetic and epigenetic factors may be causally involved in the development of NAFLD in children. Diet composition and in particular simple carbohydrate intake (especially high fructose intake) was reported as factors that may promote the development of NAFLD, whereas nondigestible carbohydrates (dietary fiber), by affecting gut microbiota, may favor the integrity of gut wall and reduce inflammation, opposing this process [30].

This study aimed to examine whether nutrient intakes in childhood are associated with abdominal and hepatic fat depots later in adolescence. Using data from a longitudinal cohort, they showed that nutrient intakes in childhood (~10 years of age) were differentially associated with different types of abdominal and ectopic fat deposition later in adolescence; specifically, higher unsaturated fat intake predicted abdominal subcutaneous adipose tissue, higher animal protein intake predicted visceral adipose tissue, and higher starch intake predicted hepatic fat.

A previous study found that decreases in fiber and vegetable protein and increases in saturated fat intake between childhood and adolescence interact with the PNPLA3 variant risk allele (a strong genetic risk factor for hepatic fat) to predict higher hepatic fat in adolescence [31]. However, Cohen et al. did not find an association between childhood fiber intake and adolescent hepatic fat, but this may be biased by the higher starch intake that is usually low in fiber. Interestingly, they also did not find associations between childhood total sugar intake and adolescent abdominal visceral adipose tissue or hepatic fat, which conflicts with studies in children showing that dietary sugar restriction was associated with reductions in these body fat depots [32, 33]. These discrepancies may be due to differences in sample characteristics, because most previous studies have focused on youth with obesity, compared with the generally healthy sample of youth in the current study. It may also suggest that intakes of the different nutrients (i.e., sugar, fiber) more proximal to adolescence may be more relevant to body fat partitioning patterns than intakes earlier in childhood.

The strengths of the study are the prospective design with the longitudinal of approximately 6 years follow-up between exposure and outcome and the assessments of abdominal and hepatic fat mass by magnetic resonance imaging. Its limitations include the reliance on self-reported dietary intake data, which can be prone to social desirability bias, particularly in individuals with obesity and may contribute to dietary

underreporting; and also, the observational nature of this study, which limits causal inference.
Nevertheless, the findings of this study may be used to plan dietary interventions aiming to promote a healthier body fat distribution in youth.

Mediterranean diet and genetic determinants of obesity and metabolic syndrome in European children and adolescents

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Comments: MD is characterized by the prevalent consumption of fruits, vegetables, whole grain cereals, legumes, nuts, and seeds, with olive oil as the main source of added fat. The MD is associated with significant health benefits, with higher MD adherence at early ages associated with a lower risk of developing obesity during childhood [34]. Research indicates a major role for genetic susceptibility to obesity and the MetS. Therefore, predisposing genetic factors for development of obesity and the associated metabolic complications may change the "protecting effect" of the MD. Understanding the biological impact of gene-nutrient interactions can provide a key insight into the pathogenesis and progression of diet-related polygenic disorders, including MetS. Indeed, in European youth, the individual's genetic profile has been previously observed to modulate the effect of MD in terms of obesity and MetS [35].
The current study is based on a systematic literature search with evaluation of the impact of genetic factors in the ability of MD to reduce the obesity and MetS risk, and to observe the impact of MD on the genetic predisposition to obesity and MetS. The present review has shown that gene-diet interaction effects in early life remain deeply understudied in young individuals of European origin. Only one study evaluated these issues in the pediatric age group [35]. This study was carried out under the HELENA study, a cross-sectional multicentric study in European adolescents. Its main findings showed that the influence of high MD adherence on adiposity and MetS was only observed if a limited number of risk alleles were present. In addition, the gene-MD interaction effect showed sex-specific differences, being higher in females than in males.
The strengths of that study are the large sample of patients (n = 605) included and, due to the multicenter design including participants from 10 European cities, the researchers have been provided with large datasets from diversely distributed adolescent populations across Europe. Its limitation was the cross-sectional design that does not allow to establish a cause-effect relationship. Moreover, only selected risk loci were available in the HELENA study. The constructed obesity genetic risk score of the

HELENA study does not include potential rarer variants that may emerge when genome-wide association studies are carried out.
Since the majority of the studies evaluated in the present review were conducted in European adults, it is hard to get to conclusion about the pediatric population. Nevertheless, as MetS and obesity may occur from childhood to adulthood, early detection is essential to elaborate on health prevention programs among the young population to effectively reduce the risk of cardiometabolic diseases, and the adherence to MD can modify the risk. The genes-diet interaction effect on MetS is gender dependent with a stronger effect in females than in males. Thus, personalized nutritional approach, wherein the genetic profile may determine the responsiveness of patients to a specific diet, may be recommended as a possible therapeutic measure to reduce the risk of MetS.

Vitamin D supplementation and cardiometabolic risk factors among diverse school children: a randomized clinical trial

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Am J Clin Nutr 2022;115:73–78
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Comments: Along with the high prevalence of obesity and MetS in pediatric patients, children and adolescents in the majority of countries are diagnosed with vitamin D deficiency. There is growing evidence linking vitamin D deficiency to various negative health outcomes including hypertension, diabetes, and cardiovascular diseases. Low vitamin D concentrations are associated with markers of subclinical arteriosclerosis, including arterial endothelial dysfunction and increased arterial stiffness [36] that are predictors for future cardiovascular events [37]. Therefore, an increasing attention to the effect of vitamin D supplementation on cardiometabolic risk markers in children and adolescents has been gained recently. A new meta-analysis of randomized controlled trials examined the effect of vitamin D supplementation (for 6 weeks to 6 months) on cardiometabolic risk markers in children and adolescents. It indicates that vitamin D supplementation appeared to have a beneficial effect on reducing fasting glucose and triglycerides level with total vitamin D supplementation ≥200,000 IU but without a significant effect on HDL cholesterol, LDL cholesterol, TC, BMI, blood pressure, and waist circumferences levels in children and adolescents [38].
The recent reviewed randomized clinical trial study examined the effect of 3 different daily dosages of vitamin D (600, 1,000, or 2,000 IU) for 6 months, with subsequent follow-up of another 6 months on cardiometabolic risk factors among children at risk of deficiency. Of note, over one third (39.6%) of the children were vitamin D inadequate (<20 ng/mL). In contrast to the findings of the meta-analysis, the researchers of

this study found that vitamin D supplementation demonstrated generally positive effects on HDL cholesterol, LDL cholesterol, and TC, especially at the lower dosage of 600 IU/day, with several significant changes persisting during the postsupplementation period.

The strengths of the study include its randomized controlled design and the large sample of participants of healthy children of diverse racial/ethnic backgrounds who are at risk of poor cardiometabolic health. The limitation of the study includes the self-reported dietary vitamin D intake that may be subject to reporting error.

Yet, together with the other advantages of vitamin D supplementation, optimization of children's vitamin D status may improve their cardiovascular health.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 70–85 (DOI: 10.1159/000527944)

Epigenetics, Nutrition and Growth

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Introduction

Epigenetics comprises different heritable biochemical DNA modifications that can alter gene transcription into RNA, and hence the degree of formation of the respective gene product, while the sequence of DNA is preserved. Key mechanisms of epigenetic DNA changes are histone modifications and DNA methylation, with the latter being the most widely studied epigenetic mechanism in human population. DNA methylation occurs at DNA regions where cytosine is followed by guanine, which are referred to as CpG sites. Early-life periods including embryonic, fetal, and infant development represent time windows when the human epigenome shows a high degree of plasticity and is particularly susceptible to external exposures. Environmental and nutritional cues appear to play a key role in regulating epigenetic processes, which may induce long-lasting effects of later tissue function, health, and disease risks. Therefore, exploration of epigenetic mechanisms, susceptible time windows and population or patient groups, relevant exposures, effects and effect sizes, and their fluidity or persistence are of great interest. For this chapter, a search was performed in the US National Library of Medicine (Pub Med) with the search terms "(epigenetic*) AND ((nutrit*) OR (growth))" and filter "humans" for the years 2021 and 2022. The hits were hand searched by the author, and the publications shown below were subjectively selected based on interest and relevance to human nutrition and growth.

Key articles reviewed for this chapter

Examining the association between adiposity and DNA methylation: a systematic review and meta-analysis

Do WL, Gohar J, McCullough LE, Galaviz KI, Conneely KN, Narayan KMV

Obes Rev 2021;22:e13319

Fat mass and obesity-associated (FTO) gene epigenetic modifications in gestational diabetes: new insights and possible pathophysiological connections

Franzago M, Fraticelli F, Marchioni M, Di Nicola M, Di Sebastiano F, Liberati M, Stuppia L, Vitacolonna E

Acta Diabetol 2021;58:997–1007

Genome-wide placental gene methylations in gestational diabetes mellitus, fetal growth, and metabolic health biomarkers in cord blood

Wang WJ, Huang R, Zheng T, Du Q, Yang MN, Xu YJ, Liu X, Tao MY, He H, Fang F, Li F, Fan JG, Zhang J, Briollais L, Ouyang F, Luo ZC for the Shanghai Birth Control

Front Endocrinol (Lausanne) 2022;13:875180

Maternal glycemic dysregulation during pregnancy and neonatal blood DNA methylation: meta-analyses of epigenome-wide association studies

Tobi EW, Juvinao-Quintero DL, Ronkainen J, Ott R, Alfano R, Canouil M, Geurtsen ML, Khamis A, Küpers LK, Lim IY, Perron P, Pesce G, Tuhkanen J, Starling AP, Andrew T, Binder E, Caiazzo R, Chan JKY, Gaillard R, Gluckman PD, Keikkala E, Karnani N, Mustaniemi S, Nawrot TS, Pattou F, Plusquin M, Raverdy V, Tan KH, Tzala E, Raikkonen K, Winkler C, Ziegler AG, Annesi-Maesano I, Bouchard L, Chong YS, Dabelea D, Felix JF, Heude B, Jaddoe VWV, Lahti J, Reimann B, Vääräsmäki M, Bonnefond A, Froguel P, Hummel S, Kajantie E, Jarvelin MR, Steegers-Theunissen RPM, Howe CG, Hivert MF, Sebert S

Diabetes Care 2022;45:614–623

Effect of an antenatal diet and lifestyle intervention and maternal BMI on cord blood DNA methylation in infants of overweight and obese women: the LIMIT randomised controlled trial

Louise J, Deussen AR, Koletzko B, Owens J, Saffery R, Dodd JM

PLoS One 2022;17:e0269723

Placental multi-omics integration identifies candidate functional genes for birthweight

Tekola-Ayele F, Zeng X, Chatterjee S, Ouidir M, Lesseur C, Hao K, Chen J, Tesfaye M, Marsit CJ, Workalemahu T, Wapner R

Nat Commun 2022;13:2384

Epigenome-wide contributions to individual differences in childhood phenotypes: a GREML approach

Neumann A, Pingault JB, Felix JF, Jaddoe VWV, Tiemeier H, Cecil C, Walton E

Clin Epigenetics 2022;14:53

DNA methylation mediates the association between breastfeeding and early-life growth trajectories

Briollais L, Rustand D, Allard C, Wu Y, Xu J, Rajan SG, Hivert MF, Doyon M, Bouchard L, McGowan PO, Matthews S, Lye S

Clin Epigenetics 2021;13:231

Meta-analysis of epigenome-wide association studies in newborns and children show widespread sex differences in blood DNA methylation

Solomon O, Huen K, Yousefi P, Küpers LK, González JR, Suderman M, Reese SE, Page CM, Gruzieva O, Rzehak P, Gao L, Bakulski LM, Novoloaca A, Allard C, Pappa I, Llambrich M, Vives M, Jima DD, Kvist T, Baccarelli A, White C, Rezwan FI, Sharp GC, Tindula G, Bergström A, Grote V, Dou JF, Isaevska E, Magnus MC, Corpeleijn E, Perron P, Jaddoe VWV, Nohr EA, Maitre L, Foraster M, Hoyo C, Håberg SE, Lahti J, DeMeo DL, Zhang H, Karmaus W, Kull I, Koletzko B, Feinberg JI, Gagliardi L, Bouchard L, Ramlau-Hansen CH, Tiemeier H, Santorelli G, Maguire RL, Czamara D, Litonjua AA, Langhendries JP, Plusquin M, Lepeule J, Binder EB, Verduci E, Dwyer T, Carracedo A, Ferre N, Eskenazi B, Kogevinas M, Nawrot TS, Munthe-Kaas MC, Herceg Z, Relton C, Melén E, Gruszfeld D, Breton C, Fallin MD, Ghantous A, Nystad W, Heude B, Snieder H, Hivert MF, Felix JF, Sørensen TIA, Bustamante M, Murphy SK, Raikkönen K, Oken E, Holloway JW, Arshad SH, London SJ, Holland N

Mutat Res Rev Mutat Res 2022;789:108415

DNA methylation in newborns conceived by assisted reproductive technology

Håberg SE, Page CM, Lee Y, Nustad HE, Magnus MC, Haftorn KL, Carlsen EØ, Denault WRP, Bohlin J, Jugessur A, Magnus P, Gjessing HK, Lyle R

Nat Commun 2022;13:1896

Epigenome-wide association study of bronchopulmonary dysplasia in preterm infants: results from the discovery-BPD program

Wang X, Cho HY, Campbell MR, Panduri V, Coviello S, Caballero MT, Sambandan D, Kleeberger SR, Polack FP, Ofman G, Bell DA

Clin Epigenetics 2022;14:57

Prenatal exposure to phthalates and peripheral blood and buccal epithelial DNA methylation in infants: an epigenome-wide association study

England-Mason G, Merrill SM, Gladish N, Moore SR, Giesbrecht GF, Letourneau N, MacIsaac JL, MacDonald AM, Kinniburgh DW, Ponsonby AL, Saffery R, Martin JW, Kobor MS, Dewey D

Environ Int 2022;163:107183

Cumulative risks predict epigenetic age in adult survivors of extremely low birth weight

Mathewson KJ, McGowan PO, de Vega WC, Morrison KM, Saigal S, Van Lieshout RJ, Schmidt LA

Dev Psychobiol 2021;63(Suppl 1):e22222

Altered DNA methylation at age-associated CpG sites in children with growth disorders: impact on age estimation?

Mayer F, Becker J, Reinauer C, Böhme P, Eickhoff SB, Koop B, Gündüz T, Blum J, Wagner W, Ritz-Timme S

Int J Legal Med 2022;136:987–996

Differentially methylated CpGs in response to growth hormone administration in children with idiopathic short stature

Shao X, Le Stunff C, Cheung W, Kwan T, Lathrop M, Pastinen T, Bougnères P

Clin Epigenetics 2022;14:65

Examining the association between adiposity and DNA methylation: a systematic review and meta-analysis

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Comments: This is a very informative systematic review indicating significant associations of more than 50 methylated CpG sites in blood cells with body mass index (BMI), many of which have been linked to type 2 diabetes, cardiovascular disease, Crohn's disease, and depression. Since much of the data used are based on cross-sectional studies, no firm conclusions can be drawn on the direction of causality, i.e., whether methylation of specific CpG sites modulates BMI evolution or whether differences in BMI have an impact on DNA methylation, which was previously proposed based on longitudinal studies in cohorts of children.

Fat mass and obesity-associated (FTO) gene epigenetic modifications in gestational diabetes: new insights and possible pathophysiological connections

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Acta Diabetol 2021;58:997–1007

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https://pubmed.ncbi.nlm.nih.gov/33743080/

Comments: Gestational diabetes mellitus (GDM) is a very common complication of pregnancy, with a recent increase of its incidence observed along with an increasing prevalence of overweight and obesity in pregnant women. GDM is associated with adverse later health outcomes both in the mother, e.g., diabetes mellitus type 2, metabolic and cardiovascular disease, and in the offspring, e.g., high birthweight, and increased later risk of obesity and noncommunicable diseases. Expression of the *FTO* gene has previously been reported to be associated with fetal weight and length, and with placental weight. This study in a relatively small sample of 60 pregnant women (33 with

GDM and 27 without GDM) with a detailed characterization of clinical parameters, lifestyle, and diet analyzed DNA methylation of 4 CpGs within the promoter of the *FTO* gene from washed placental tissue samples. Interestingly, the results show that the 4 CpGs were mainly unmethylated in both patient groups. Methylation was similar at the maternal and the fetal sides of the placenta. Differences in the methylation patterns occurred in women exposed to tobacco smoke during pregnancy, in line with previous studies reporting a marked effect of smoke exposure during pregnancy on DNA methylation. In contrast, GDM was not associated with placental DNA methylation in the *FTO* gene.

Genome-wide placental gene methylations in gestational diabetes mellitus, fetal growth, and metabolic health biomarkers in cord blood

Wang WJ[1,2,3], Huang R[2], Zheng T[4], Du Q[1,5], Yang MN[1], Xu YJ[1], Liu X[1], Tao MY[1], He H[1], Fang F[1], Li F[1], Fan JG[6], Zhang J[1], Briollais L[7], Ouyang F[1], Luo ZC[1,2] for the Shanghai Birth Control

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Front Endocrinol (Lausanne) 2022;13:875180

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https://pubmed.ncbi.nlm.nih.gov/35721735/

Comments: In this study of 30 placentas of Chinese women with GDM paired with 30 placentas of women without GDM, GDM was associated with DNA methylation changes in a number of placental genes. However, these placental gene methylations were uncorrelated to the measured metabolic health biomarkers including fetal growth factor measures, and cord blood leptin and adiponectin.

Maternal glycemic dysregulation during pregnancy and neonatal blood DNA methylation: meta-analyses of epigenome-wide association studies

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Diabetes Care 2022;45:614–623
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Comments: This meta-analysis combined data from 7 cohort studies with inclusion of a large number of pregnant women from Europe, North America, and Singapore with available data on cord blood DNA to explore associations with continuous maternal glucose measurements, insulin, and area under the curve of glucose measures after an oral glucose tolerance test conducted during pregnancy. No evidence of robust associations between maternal prenatal glucose and insulin levels and offspring DNA methylation in cord blood was revealed, which could be interpreted to refute the concept that maternal hyperglycemia during pregnancy would mediate childhood health phenotypes via changes in DNA methylation. But the meta-analysis of the area under the curve of glucose measures showed inverse associations with cord blood DNA methylation at 2 CpG sites in the thioredoxin interacting protein gene (TXNIP), which were only observed among women without GDM. Of interest, exposure to higher maternal fasting glucose, higher HbA1c, and maternal type 1 diabetes was also associated with a lower DNA methylation in TXNIP in cord blood. These observations should prompt further exploration of a potential pathway between prenatal exposure to hyperglycemia exposure, DNA methylation at TXNIP, and later offspring health.

Effect of an antenatal diet and lifestyle intervention and maternal BMI on cord blood DNA methylation in infants of overweight and obese women: the LIMIT randomised controlled trial

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PLoS One 2022;17:e0269723
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Comments: Most analyses associating DNA methylation with exposures in pregnancy are based on observational studies which cannot firmly establish cause-and-effect relationships. Therefore, DNA methylation studies in randomized controlled intervention trials addressing dietary or lifestyle exposures are of particular value. This publication reports on cord blood DNA methylation analyses in offspring of women who participated in the randomized controlled LIMIT trial which explored the effects of an antenatal diet and lifestyle intervention for women entering pregnancy with overweight. The intervention targeted the reduction of dietary sugar and saturated fat intake and enhanced physical activity. No probes were significantly differentially methylated between the Lifestyle Advice and Standard Care groups, and there was no evidence for effect modification by maternal BMI. The top 10 differentially methylated probes by *p* value were spread across the genome and showed small effect sizes. The top 10 differentially methylated probes by log-fold change did not overlap with the top 10 by *p* value, and again effect sizes were relatively small. Overall, an antenatal lifestyle intervention or maternal early pregnancy BMI did not affect DNA methylation in cord blood, which suggests that other causal pathways are primarily responsible for linking maternal and childhood obesity.

Placental multi-omics integration identifies candidate functional genes for birthweight

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Nat Commun 2022;13:2384
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Comments: Tekola-Ayele et al. evaluated genome, DNA methylation, and gene expression from placenta samples of 2,802 women participating in a cohort study in the USA. Some 286 single-nucleotide polymorphisms (SNPs) were associated with birthweight, and 23 co-occurring SNPs were associated with both placental gene expression and DNA methylation. Causal inference analyses found evidence of a causal relationship between birthweight SNP altering DNA methylation in the placenta, which in turn causally influences gene expression in 88 of 197 triplets consisting of 15 SNPs, 17 protein coding genes, and 81 DNA methylation sites. The results obtained suggest that the effect of the genetic variants on birthweight is possibly mediated by their direct regulatory influence on epigenetic and transcriptomic changes in the placenta.

Epigenome-wide contributions to individual differences in childhood phenotypes: a GREML approach

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Clin Epigenetics 2022;14:53

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https://pubmed.ncbi.nlm.nih.gov/35440009/

Comments: In this impressive study combining data from the British ALSPAC and the Dutch Generation R studies, Neumann et al. aimed to assess the overall contribution of genome-wide cord blood cell DNA methylation data towards gestational age, birthweight, and health outcomes in later childhood. Methylation data were found to explain a third of the variance for gestational age, and a much lesser degree of the variance of birthweight, while BMI, intelligence quotient, or attention-deficit hyperactivity symptoms at school age were not explained by cord blood DNA methylation.

DNA methylation mediates the association between breastfeeding and early-life growth trajectories

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Clin Epigenetics 2021;13:231

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Comments: Breastfeeding is universally considered as the optimal way of infant feeding. It has been associated with numerous health effects, including mediation of growth in infancy and beyond. In a small number of previous studies, breastfeeding and its duration have been associated with DNA methylation changes, but the available information remains rather limited. In this study, Briollais et al. report on the analysis of DNA methylation data from blood cells of 1,018 mother-offspring pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) that were related to breastfeeding information reported by mothers, and growth measures. The duration of exclusive breastfeeding was associated with DNA methylation changes particularly during the first 3 years of life, and with lesser effect sizes at later ages up to 17 years. DNA methylation corresponding to 3–5 months of exclusive breastfeeding was associated with slower BMI growth the first 6 years of life, when compared to absence of exclusive breastfeeding, and in a dose-response manner with the duration of exclusive breastfeeding, but this mediation effect disappeared after 6 years of age. The CpG sites with highest levels of statistical significance were related to the AMP-activated protein kinase (AMPK) pathway, the insulin signaling pathway, and endocytosis in girls, and in boys to pathways related to cancer. The findings suggest that the mechanisms by which breastfeeding can reduce later overweight and obesity might be mediated through hypo- and hypermethylation of DNA early in life.

Meta-analysis of epigenome-wide association studies in newborns and children show widespread sex differences in blood DNA methylation

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Comments: Several previous studies have suggested sex differences of DNA methylation in placenta, cord blood, and blood samples obtained in childhood. This large meta-analysis combined cord blood cell DNA methylation data of more than 8,000 neonates from as many as 40 birth cohort studies. Perhaps not surprisingly, 99.8% of the more than 9,600 CpG sites on the X chromosome were significantly differentially methylated between males and females. Also, almost 47,000 of the nearly 400,000 tested autosomal CpG sites showed significantly different DNA methylation, after adjusting for white blood cell proportions and batch, with about two thirds of the sites showing lower methylation levels in male neonates. Sex differences were enriched in genes involved in biological pathways important for development, and risk of cancer, psychiatric disorders, and cardiovascular phenotypes. It is tempting to speculate that early-life DNA methylation differences may represent a potential mechanism regulating differential disease risk by sex.

DNA methylation in newborns conceived by assisted reproductive technology

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Nat Commun 2022;13:1896

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Comments: Assisted reproduction has markedly increased in use in recent years. It has been associated with different adverse pregnancy outcomes and adverse long-term health effects in the offspring affecting neurodevelopment, cardiovascular health, metabolism, growth, and risk of malignant diseases. It remains to be resolved to which extent such effects are due to the assisted reproduction interventions, or due to risk factors associated with reduced parental fertility. The authors used DNA samples obtained from large groups of couples from the Norwegian Mother, Father and Child Cohort study, either with children that were naturally conceived or conceived with assisted reproduction, as well as cord blood of the newborn infants. In neonates born after assisted reproduction, 74% of CpGs were hypomethylated, whereas no such shift was found in the parents. Differentially methylated CpGs in the 2 groups of neonates were annotated to 176 genes, where mutations in 14 of these cause Mendelian disorders, 9 of them with a neurological phenotype, suggesting potential implications for long-term development and health.

Epigenome-wide association study of bronchopulmonary dysplasia in preterm infants: results from the discovery-BPD program

Wang X[1], Cho HY[1], Campbell MR[1], Panduri V[2], Coviello S[3], Caballero MT[3,4], Sambandan D[1,7], Kleeberger SR[1], Polack FP[3,5], Ofman G[3,6], Bell DA[1]

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Clin Epigenetics 2022;14:57

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https://pubmed.ncbi.nlm.nih.gov/35484630/

Comments: Previous studies in animals and observational studies in humans reported an association of prenatal psychosocial stress with altered DNA methylation and behavioral outcomes in the offspring. In this small but rather interesting controlled intervention study, pregnant adolescents were randomized to either care as usual or to participation in a home-visit program by trained nurses from the first 16 weeks of pregnancy until the child's age of 24 months. The program was designed to strengthen maternal competences for warm and responsive care, facilitate child-centered interactions and improve bonding with the infant, and improve parenting skills by modeling. The results suggest an effect of the prenatal intervention part on differential DNA methylation of cord blood cells, with causal mediation analyses suggesting a mediating effect on cognition at age 12 months. Further studies should be performed to replicate the apparent impact of maternal prenatal psychosocial intervention on neurodevelopmental outcomes mediated by epigenetic mechanisms.

Prenatal exposure to phthalates and peripheral blood and buccal epithelial DNA methylation in infants: an epigenome-wide association study

England-Mason G[1,2], Merrill SM[3,4,5], Gladish N[3,4,5], Moore SR[3,4,5], Giesbrecht GF[1,2,6,7], Letourneau N[1,2,7,8,9,10], MacIsaac JL[3,4,5], MacDonald AM[11], Kinniburgh DW[11,12], Ponsonby AL[13], Saffery R[13], Martin JW[14], Kobor MS[3,4,5,15], Dewey D[1,2,7,10]

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Environ Int 2022;163:107183
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https://pubmed.ncbi.nlm.nih.gov/35325772/

Comments: Phthalate esters are chemicals that have been widely used as plasticizers to increase the flexibility, transparency, and durability of plastic materials, and in many other products, e.g., liquid soaps, cosmetics, and medical devices and tubing. Concerns about apparent adverse health effects have been raised. This study in Canadian mother-infant pairs shows maternal high- and low-molecular-weight phthalate exposure in pregnancy associated with differential DNA methylation of infant blood and buccal epithelial cells at the age of 3 months after birth. Thus altered DNA methylation could be one mechanism by which prenatal phthalate exposure influences health and disease later in life. The results also support a precautionary approach, with measures to reduce the ubiquitous human exposure to phthalates as much as feasible.

Cumulative risks predict epigenetic age in adult survivors of extremely low birth weight

Mathewson KJ[1], McGowan PO[2], de Vega WC[2], Morrison KM[3], Saigal S[3], Van Lieshout RJ[4], Schmidt LA[1]

[1]Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, ON, Canada; [2]Department of Biological Sciences, Cell and Systems Biology, Psychology, and Physiology, University of Toronto, Toronto, ON, Canada; [3]Department of Pediatrics, McMaster University, Hamilton, ON, Canada; [4]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

Dev Psychobiol 2021;63(Suppl 1):e22222

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https://pubmed.ncbi.nlm.nih.gov/34964497/

Comments: Chronological age and biological age are associated with changes in DNA methylation. In the second decade of the 21st century, Steven Horvath and coworkers developed the concept of an epigenetic clock based on a set of methylation markers. Several epigenetic clocks have since been developed and associated with age-related phenotypes. Mathewson et al. assessed epigenetic age based on DNA methylation at 353 CpG sites in 45 young adults born with extremely low birthweight (ELBW) and 47 born with normal birthweight. Epigenetic age was more than 2 years higher in ELBW subjects at the chronological age of 32 years, which may mediate the reported increased risk of adverse adult health outcomes in people born with ELBW.

Altered DNA methylation at age-associated CpG sites in children with growth disorders: impact on age estimation?

Mayer F[1], Becker J[1], Reinauer C[2], Böhme P[1], Eickhoff SB[3,4], Koop B[1], Gündüz T[1], Blum J[1], Wagner W[5], Ritz-Timme S[1]

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Int J Legal Med 2022;136:987–996

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https://pubmed.ncbi.nlm.nih.gov/35551445/

Comments: In forensic medicine, the age estimation based on the epigenetic clock approach applying DNA methylation analysis has become widely used. This observational study reports a significant impact of different childhood growth disorders on epigenetic DNA methylation. Age-related DNA methylation analysis appears to be feasible also in children; however, it tended to overestimate age in children with growth disorders. It appears desirable that future studies explore potential differences between various types of childhood growth disorders in greater detail.

Differentially methylated CpGs in response to growth hormone administration in children with idiopathic short stature

Shao X[1], Le Stunff C[2], Cheung W[3], Kwan T[4], Lathrop M[4], Pastinen T[3], Bougnères P[2]

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Clin Epigenetics 2022;14:65

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https://pubmed.ncbi.nlm.nih.gov/35585611/

Comments: Considerable inter-individual differences exist between children receiving recombinant human growth hormone (rhGH) with respect to the response to treatment. This study explored whether rhGH produced epigenetic marks on the methylome of peripheral blood mononuclear cells, and their inter-individual variation, after a treatment duration ranging from 6 to 38.4 months. Comparing samples before and after treatment, 267 differentially methylated CpGs were identified in 265 genes which were enriched in pathways related to cell differentiation, system development, and growth-related pathways such as endoderm differentiation, adipocytokine signaling, PPAR alpha, and TGF-beta signaling pathways. However, significance was lost after correcting for multiple testing (false discovery rate). The authors also found marked intra-individual responses of DNA-methylation to long-term rhGH treatment. These results indicate the potential that effects of rhGH therapy might be partly mediated by epigenetic regulation, and that this might contribute to inter-individual variation in response to growth hormone.

Acknowledgments

This work has been financially supported in part by European Joint Programming Initiative Projects NutriPROGRAM and German Federal Ministry of Education and Research – 01EA1904. Further support was provided by BK, the Else Kröner Senior Professor of Paediatrics at LMU – University of Munich, financially supported by Else Kröner-Fresenius-Foundation, LMU Medical Faculty and LMU University Hospitals.

Conflict of Interest Statement

No conflict of interest is declared with respect to the contents of this manuscript, with no circumstances involving the risk that the professional judgment or acts of primary interest may be unduly influenced by a secondary interest.

Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 86–113 (DOI: 10.1159/000527945)

Nutrition and Growth in Preterm and Term Infants

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Introduction

Nutrition and growth of preterm infants is attracting a lot of attention. This year, we decided to address 3 topics on which several interesting studies have been published. By including papers on the indications and electrolyte composition of parenteral nutrition (PN), and on necrotizing enterocolitis (NEC), we thought to provide you with ample interesting topics that might change your view on how to take care of premature infants at your ward.

For term infants, the review addressed 4 different topics: breastfeeding, breast milk substitutes, food allergy (FA), and complementary feeding (CF).

Key articles reviewed for this chapter

Preterm Infants

Indications of Parenteral Nutrition

Early versus later initiation of parenteral nutrition for very preterm infants: a propensity score-matched observational study
Uthaya S, Longford N, Battersby C, Oughham K, Lanoue J, Modi N
Arch Dis Child Fetal Neonatal Ed 2022;07:137–142

Outcomes in relation to early parenteral nutrition use in preterm neonates born between 30 and 33 weeks' gestation: a propensity score matched observational study
Webbe JW, Longford N, Battersby C, Oughham K, Uthaya SN, Modi N, Gale C
Arch Dis Child Fetal Neonatal Ed 2022;107:131–136

Use of parenteral nutrition in the first postnatal week in England and Wales: an observational study using real-world data
Webbe J, Battersby C, Longford N, Oughham K, Uthaya S, Modi N, Gale C
BMJ Paediatr Open 2022;6:e001543

Association between early amino acid intake and full-scale IQ at age 5 years among infants born at less than 30 weeks' gestation
Rozé JC, Morel B, Lapillonne A, Marret S, Guellec I, Darmaun D, Bednarek N, Moyon T, Marchand-Martin L, Benhammou V, Pierrat V, Flamant C, Gascoin G, Mitanchez D, Cambonie G, Storme L, Tosello B, Biran V, Claris O, Picaud JC, Favrais G, Beuchée A, Loron G, Gire C, Durrmeyer X, Gressens P, Saliba E, Ancel PY
JAMA Netw Open 2021;4:e2135452

Electrolyte Composition of Parenteral Nutrition

Refeeding syndrome in the neonatal intensive care unit
Bradford CV, Cober MP, Miller JL
J Pediatr Pharmacol Ther 2021;26:771–782

Early vs late initiation of sodium glycerophosphate: impact on hypophosphatemia in preterm infants <32 weeks
Ozer Bekmez B, Oguz SS
Clin Nutr 2022;41:415–423

Higher parenteral electrolyte intakes in preterm infants during first week of life: effects on electrolyte imbalances
Späth C, Sjostrom ES, Domellöf M
J Pediatr Gastroenterol Nutr 2022;75:e53–e59

Necrotizing Enterocolitis

Discriminating necrotising enterocolitis and focal intestinal perforation
Berrington J, Embleton ND
Arch Dis Child Fetal Neonatal Ed 2022;107:336–339

Time of onset of necrotizing enterocolitis and focal perforation in preterm infants: impact on clinical, surgical, and histological features
Berrington JE, Embleton ND
Front Pediatr 2021;9:724280

A critical evaluation of current definitions of necrotizing enterocolitis
Lueschow SR, Boly TJ, Jasper E, Patel RM, McElroy S
J Pediatr Res 2022;91:590–597

Spontaneous intestinal perforation (SIP) will soon become the most common form of surgical bowel disease in the extremely low birth weight (ELBW) infant
Swanson JR, Hair A, Clark RH, Gordon PV
J Perinatol 2022;42:423–429

Initial laparotomy versus peritoneal drainage in extremely low birthweight infants with surgical necrotizing enterocolitis or isolated intestinal perforation: a multicenter randomized clinical trial
Blakely ML, Tyson JE, Lally KP, Hintz SR, Eggleston B, Stevenson DK, Besner GE, Das A, Ohls RK, Truog WE, Nelin LD, Poindexter BB, Pedroza C, Walsh MC, Stoll BJ, Geller R, Kennedy KA, Dimmitt RA, Carlo WA, Cotten CM, Laptook AR, Van Meurs KP, Calkins KL, Sokol GM, Sanchez PJ, Wyckoff MH, Patel RM, Frantz ID 3rd, Shankaran S, D'Angio CT, Yoder BA, Bell EF, Watterberg KL, Martin CA, Harmon CM, Rice H, Kurkchubasche AG, Sylvester K, Dunn JCY, Markel TA, Diesen DL, Bhatia AM, Flake A, Chwals WJ, Brown R, Bass KD, St Peter SD, Shanti CM, Pegoli W Jr, Skarda D, Shilyansky J, Lemon DG, Mosquera RA, Peralta-Carcelen M, Goldstein RF, Vohr BR, Purdy IB, Hines AC, Maitre NL, Heyne RJ, DeMauro SB, McGowan EC, Yolton K, Kilbride HW, Natarajan G, Yost K, Winter S, Colaizy TT, Laughon MM, Lakshminrusimha S, Higgins RD, Eunice Kennedy Shriver National Institute of Child Health, Human Development Neonatal Research Network
Ann Surg 2021;274:e370–e380

NEC Prevention

Oropharyngeal colostrum therapy reduces the incidence of ventilator-associated pneumonia in very low birth weight infants: a systematic review and meta-analysis
Ma A, Yang J, Li Y, Zhang X, Kang Y
Pediatr Res 2021;89:54–62

Does oropharyngeal administration of colostrum reduce morbidity and mortality in very preterm infants? A randomised parallel-group controlled trial
Aggarwal R, Plakkal N, Bhat V
J Paediatr Child Health 2021;57:1467–1472

Efficacy and safety of enteral recombinant human insulin in preterm infants: a randomized clinical trial
Mank E, Sáenz de Pipaón M, Lapillonne A, Carnielli VP, Senterre T, Shamir R, van Toledo L, van Goudoever JB for the FIT-04 Study Group
JAMA Pediatr 2022;176:452–460

Term Infants

Breastfeeding

Associations of breastfeeding with childhood autoimmunity, allergies, and overweight: The Environmental Determinants of Diabetes in the Young (TEDDY) study

Hummel S, Weiß A, Bonifacio E, Agardh D, Akolkar B, Aronsson CA, Hagopian WA, Koletzko S, Krischer JP, Lernmark Å, Lynch K, Norris JM, Rewers MJ, She JX, Toppari J, Uusitalo U, Vehik K, Virtanen SM, Beyerlein A, Ziegler AG, TEDDY Study Group

Am J Clin Nutr 2021;114:134–142

Breastfeeding and risk of overweight in childhood and beyond: a systematic review with emphasis on sibling-pair and intervention studies

Dewey KG, Güngör D, Donovan SM, Madan EM, Venkatramanan S, Davis TA, Kleinman RE, Taveras EM, Bailey RL, Novotny R, Terry N, Butera G, Obbagy J, de Jesus J, Stoody E

Am J Clin Nutr 2021;114:1774–1790

Osteopathic manipulative treatment to improve exclusive breast feeding at 1 month

Danielo Jouhier M, Boscher C, Roze JC, Cailleau N, Chaligne F, Legrand A, Flamant C, Muller JB, NEOSTEO osteopath study group

Arch Dis Child Fetal Neonatal Ed 2021;106:F591–F595

Breast Milk Substitutes

Conduct and reporting of formula milk trials: systematic reviews

Helfer B, Leonardi-Bee J, Mundell A, Parr C, Ierodiakonou D, Garcia-Larsen V, Kroeger CM, Dai Z, Man A, Jobson J, Dewji F, Kunc M, Bero L, Boyle RJ

BMJ 2021;375:n2202

Lactoferrin reduces the risk of respiratory tract infections: a meta-analysis of randomized controlled trials

Ali AS, Hasan SS, Kow CS, Merchant HA

Clin Nutr ESPEN 2021;45:26–32

Infant formulas with postbiotics: an updated systematic review

Szajewska H, Kołodziej M, Skorka A, Piescik-Lech M

J Pediatr Gastroenterol Nutr 2022;74:823–839

Food Allergy

Food allergy across the globe

Sampath V, Abrams EM, Adlou B, Akdis C, Akdis M, Brough HA, Chan S, Chatchatee P, Chinthrajah RS, Cocco RR, Deschildre A, Eigenmann P, Galvan C, Gupta R, Hossny E, Koplin JJ, Lack G, Levin M, Shek LP, Makela M, Mendoza-Hernandez D, Muraro A, Papadopoulous NG, Pawankar R, Perrett KP, Roberts G, Sackesen C, Sampson H, Tang MLK, Togias A, Venter C, Warren CM, Wheatley LM, Wong GWK, Beyer K, Nadeau KC, Renz H

J Allergy Clin Immunol 2021;148:1347–1364

Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial

Skjerven HO, Lie A, Vettukattil R, Rehbinder EM, LeBlanc M, Asarnoj A, Carlsen KH, Despriee ÅW, Färdig M, Gerdin SW, Granum B, Gudmundsdóttir HK, Haugen G, Hedlin G, Håland G, Jonassen CM, Landrø L, Mägi CO, Olsen IC, Rudi K, Saunders CM, Skram MK, Staff AC, Söderhäll C, Tedner SG, Aadalen S, Aaneland H, Nordlund B, Lødrup Carlsen KC

Lancet 2022;399:2398–2411

Complementary Feeding

Effect of a healthy eating intervention in the first months of life on ultraprocessed food consumption at the age of 4–7 years: a randomised clinical trial with adolescent mothers and their infants

Lazzeri B, Leotti VB, Soldateli B, Giugliani ER, Monteiro CA, Martinez Steele E, Pedrotti LG, Drehmer M

Br J Nutr 2021;126:1048–1055

Starting complementary feeding with vegetables only increases vegetable acceptance at 9 months: a randomized controlled trial

Rapson JP, von Hurst PR, Hetherington MM, Mazahery H, Conlon CA

Am J Clin Nutr 2022;116:111–121

Preterm Infants

Indications of Parenteral Nutrition

In 2021 and 2022, multiple studies on whether and to which extent PN is really beneficial for preterm infants have appeared. In the next articles we will discuss some of these [1–4].

Early versus later initiation of parenteral nutrition for very preterm infants: a propensity score-matched observational study

Uthaya S, Longford N, Battersby C, Oughham K, Lanoue J, Modi N

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Arch Dis Child Fetal Neonatal Ed 2022;07:137–142

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https://pubmed.ncbi.nlm.nih.gov/34795009/

Outcomes in relation to early parenteral nutrition use in preterm neonates born between 30 and 33 weeks' gestation: a propensity score matched observational study

Webbe JW, Longford N, Battersby C, Oughham K, Uthaya SN, Modi N, Gale C

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Arch Dis Child Fetal Neonatal Ed 2022;107:131–136

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https://pubmed.ncbi.nlm.nih.gov/34548324/

Use of parenteral nutrition in the first postnatal week in England and Wales: an observational study using real-world data

Webbe J[1], Battersby C[1], Longford N[1], Oughham K[2], Uthaya S[1], Modi N[1], Gale C[1]

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BMJ Paediatr Open 2022;6:e001543

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https://pubmed.ncbi.nlm.nih.gov/36053624/

Association between early amino acid intake and full-scale IQ at age 5 years among infants born at less than 30 weeks' gestation

Rozé JC[1,2,3], Morel B[4], Lapillonne A[5], Marret S[6], Guellec I[7], Darmaun D[3], Bednarek N[8], Moyon T[3], Marchand-Martin L[9], Benhammou V[9], Pierrat V[10], Flamant C[1,2], Gascoin G[11], Mitanchez D[12], Cambonie G[13], Storme L[10], Tosello B[14], Biran V[15], Claris O[16], Picaud JC[16], Favrais G[4], Beuchée A[17], Loron G[8], Gire C[13], Durrmeyer X[18], Gressens P[19], Saliba E[4], Ancel PY[9,20]

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JAMA Netw Open 2021;4:e2135452

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https://pubmed.ncbi.nlm.nih.gov/34846527/

Comments: Uthaya and colleagues have compiled outcome data (up till corrected age 2 years) from over 65,000 preterm infants born <31 weeks' gestation in England and Wales during a 12-year period [1]. Infants were stratified whether they had their PN initiated early after birth (i.e., within the first 2 calendar days after birth, i.e., within 48 h after birth) or from after the third calendar day onward (which could in fact be already 25 h after birth), meaning that some overlap was inevitable. From the propensity score-

matched subgroups (n = 8,147 each), it was derived that there were no differences in survival without major morbidities between both groups. However, breaking down the primary outcome, authors found that mortality was lower if started early after birth with PN, whereas the incidence of several major morbidities such as late-onset sepsis, bronchopulmonary dysplasia, and retinopathy of prematurity was higher in this group.

The same group of researchers also conducted a similar approach for a similarly large data set on moderately preterm born infants, i.e., those born between 30 + 0 and 32 + 6 weeks' gestation as described in the second manuscript above [2]. The intervention was PN administered at any point in the first 7 days of postnatal life or not. Propensity score–matched infants (n = 8,146 in each group) were compared, and just like in the previous study, researchers found a lower mortality rate in the early PN group, but simultaneously more bronchopulmonary dysplasia, late-onset sepsis, NEC, and a slower growth during hospitalization. Remarkably, 8.1% of infants in the early PN group suffered NEC, which is a very high rate in these infants weighing on average 1.59 kg (SD 0.29).

Reasons for why PN was not initiated in the late PN group early after birth could not be derived. So residual confounding may always be responsible for the observed findings in cohort studies like these, no matter how large the size of a cohort may be or how many variables were controlled for. Indications and application for PN may vary from unit to unit [3], just like other therapies, treatments, and outcomes in these units. Although the cited studies controlled for regional neonatal network, individual NICU practices are difficult to control for. Thus, these studies do not provide evidence to change current practice but may provide rationale for conducting new randomized trials on the merit of PN in certain patient groups. Besides, PN may also vary in composition or quality, so that PN may not be assessed as such.

These findings could warrant what the proper indications for PN are in the neonatal population. This question is nearly automatically linked to findings from the pediatric PEPaNIC trial where it was shown that early PN after admission on a PICU resulted in adverse outcomes [5], also in the term neonatal population [6]. It is hypothesized that especially excess amino acids during an inflammatory event could also play a harmful role due to hampered autophagy processes [7]. This resulted in the recently published position paper by ESPHAN on how to implement PN during acute critical illness also in preterm infants [8, 9], which was also discussed in the last year's yearbook [10].

From France, by study design a reasonably similar article appeared in 2021 as well [4], but more or less contradicting the findings from the 2 above-discussed papers. From preterm infants born <30 weeks' gestation in the year 2011, nutritional intakes, neonatal course, and 5 years corrected age neurodevelopmental outcomes as a primary outcome were assessed. Infants were stratified by whether they had received either less or more than 3.5 g/kg per day of intravenous amino acids or enteral protein. Each propensity score–matched cohort consisted of 717 infants who were born on average at 27.2 weeks' gestation. Approximately 75% of total nutritional intake was via the parenteral route. Researchers found that infants who had the higher amino acid intakes (above 3.5 g/kg/day) had significantly higher full-scale IQ scores, a finding also confirmed by assessing amino acid intake as a continuous variable. Moreover, from a subset of 134 infants who had underwent MRI scanning at term equivalent age, positive correlations between amino acid intakes and white matter development were seen. Notably, mentioned correlations between amino acid intakes and later neurocognitive outcomes could not be repeated for the other macronutrients, i.e., lipids or carbohydrates.

Overall, it is difficult to draw a conclusion which is in accordance with all 3 very well performed propensity score–matched cohort studies. Hopefully it gives ground to new large sample sized randomized controlled trials (RCTs) on the precise indications and composition of PN in preterm infants.

Electrolyte Composition of Parenteral Nutrition

As briefly discussed in the previous section, not all PN formulations are identical of course, so that compositional differences may partly be responsible for the observed different study results. For long, the focus of PN composition was on its macronutrient composition. During the past few years, there has been more focus on the micronutrients, especially the minerals calcium and phosphate in light of a neonatal refeeding-like syndrome. Studies from recent years that brought this relatively new phenomenon to the attention were the papers by Moltu et al. [11] and Bonsante et al. [12], for example. These authors showed that providing relatively higher doses of amino acids to premature infants may result in increased anabolism, but without providing sufficient electrolytes, it may simultaneously result in adversely low concentrations of mainly potassium and phosphate. Especially those infants with fetal growth restriction or born after maternal preeclampsia seem to be at risk during the first postnatal week. Here we discuss 3 new papers on this topic [13–15].

Refeeding syndrome in the neonatal intensive care unit

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Early vs late initiation of sodium glycerophosphate: impact on hypophosphatemia in preterm infants <32 weeks

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Clin Nutr 2022;41:415–423

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Higher parenteral electrolyte intakes in preterm infants during first week of life: effects on electrolyte imbalances

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Comments: Over the years, several studies have described the problem of neonatal refeeding-like syndrome. In 2021, Bradford and colleagues published a nicely performed systematic review on all published studies so far, describing which infants are at particular risk, together with a range of observed clinical implications [13]. Hyperglycemia, prolonged mechanical ventilation, and increased incidence of sepsis and mortality form some of the frequently encountered clinical consequences of early hypophosphatemia.

Unfortunately, to date, no RCTs have been published on providing higher versus lower amounts of parenteral phosphate in order to prevent early neonatal refeeding-like syndrome. However, Ozer et al. in a nicely performed pre-post epoch cohort study compared 261 very preterm infants whether they had received 1 mmol phosphate per 100 mL in PN from birth onward or mineral-free PN during the first 48 hours after birth [14]. A marked less incidence of hypophosphatemia was seen as well as several clinical respiratory parameters such as prolonged mechanical ventilation or corticosteroid usage. Mineral-free PN should no longer be used, as also recommended by ESPGHAN advising a parenteral phosphate intake of 1.0–2.0 mmol/kg/day from birth onward, and increased within several days to 1.6–3.5 mmol/kg/day [16].

Similarly, Späth et al. compared an epoch with their "original" parenteral regimen with a more concentrated recipe which included a higher phosphate-to-amino-acid ratio as well [15]. The authors elegantly showed that providing all electrolytes from birth onward to infants born on average after 27 weeks' gestation was safe and resulted in much less serum electrolyte disturbances. Individual monitoring of phosphate serum concentrations in the first week of life, especially in those with suboptimal intrauterine growth, seems warranted, despite standard parenteral mineral provision from birth onward, as early hypophosphatemia may still be present and have direct adverse clinical consequences.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) remains a hot topic within clinical neonatology. Although the incidence drops with the use of human milk [17], the more general availability of donor human milk [18, 19], and certain strains of probiotics [20], we have not managed to banish NEC from our wards. Mortality and morbidity remain high, emphasizing that the need for ongoing mechanistic and clinical research is pivotal.

A clear classification, with a distinct differentiation between NEC and focal intestinal perforation (FIP), is important to make progress in this field, as one needs to talk the same language to be able to compare different studies and approaches. Four articles, published

during the last reviewed year for this yearbook, discuss the problems around definitions of NEC and FIP [21–24]. Blakely et al. is a long-awaited NEC surgery trial (NEST) comparing initial laparotomy versus peritoneal drainage [25].

Discriminating necrotising enterocolitis and focal intestinal perforation

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Time of onset of necrotizing enterocolitis and focal perforation in preterm infants: impact on clinical, surgical, and histological features

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Front Pediatr 2021;9:724280
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A critical evaluation of current definitions of necrotizing enterocolitis

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Spontaneous intestinal perforation (SIP) will soon become the most common form of surgical bowel disease in the extremely low birth weight (ELBW) infant

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J Perinatol 2022;42:423–429

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Initial laparotomy versus peritoneal drainage in extremely low birthweight infants with surgical necrotizing enterocolitis or isolated intestinal perforation: a multicenter randomized clinical trial

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Comments: Berrington and Embleton elegantly show the problems with the currently used classifications in 2 different articles [21, 22]. FIP and NEC had overlapping features, such as day of onset, which make discrimination difficult. They urge for caution using routinely collected data. In their study, they reviewed a large series of preterm infants born less than 32 weeks' gestation treated over a 10-year period in a tertiary neonatal unit in Newcastle, UK. Only a few features were statistically different between infants with NEC or FIP. Clinically that difference may not be very important as initial treatment is equal, but the difference is important for research purposes. A call to action was made to international panels to develop a useful and consistent classification. Such an attempt has also previously been made by an international group of experts [26]. They also took time of onset as one of the discriminating items, which is thus challenged by Berrington and Embleton. Others, like Lueschow et al., used standard statistics and machine learning to critically evaluate over 200 patients from a single center with NEC, FIP, and possible NEC across several different definitions of NEC [23].

In Lueschow's paper, newer definitions [26, 27] outperformed original Bell's criteria. Taken that into account, the article of Swanson et al. fits into this discussion as the authors state that FIP will soon be a more important surgical diagnosis than NEC [24]. They argue that rates of NEC are decreasing over recent years whereas those of FIP (abbreviated as SIP) increase. Those data are obtained from the Pediatrix/Mednax data warehouse. As Berrington emphasizes, the definition of the different diagnosis plays a pivotal role, although also the cumulative incidence decreases. Also, Swanson et al. [24] acknowledge the need for better definitions than those developed by Bell. These are data from the USA, where at that time probiotics were not used. The authors contribute predominantly the increased use of human (donor) milk to the decline.

Altogether, the discussion remains and in the next few years it will become apparent which definition we will be using. For sure we will, in future years, abandon Bell's criteria, after having served (in modified versions) for 5 decades.

In 2011, the conclusion following a Cochrane's meta-analysis by Rao et al. was: "Evidence from two RCTs suggests no significant benefits or harms of peritoneal drainage over laparotomy. However, due to the very small sample size, clinically significant differences may have easily been missed" [28]. At that time only 185 preterm or low-birth-weight infants were included. Thus, the study results of the recently published Necrotizing Enterocolitis Surgery Trial were very welcome and long awaited [25]. With a primary hypothesis that laparotomy would result in a lower rate (−15%) of death or neurodevelopmental impairment at 18–22 months corrected age, 310 infants were included. There was no overall difference in death or neurodevelopmental impairment rates in the initial laparotomy versus drainage groups (aRR = 1.0, 95% CI: 0.87–1.14). The authors hypothesize in their discussion that it is plausible that initial laparotomy would more likely benefit infants with NEC, especially those with multiple perforations and extensive intestinal necrosis and peritonitis, whereas infants with isolated intestinal perforation with a single and often small perforation may require only a peritoneal drain. However, our previous discussion demonstrated the difficulty in discriminating between those 2 entities. The need for additional laparotomy in the initial drainage group was very high, resulting in, at the end, a similar number of operations in both groups. The study took long, almost 10 years, despite 20 centers being involved. The authors state that this questions about the level of evidence that can realistically be expected or required for treatment recommendations for rare and difficult-to-study diseases. In our view, this calls for a worldwide approach for all kinds of RCTs for rare diseases or conditions and not so much abandoning well-designed large trials for rare diseases. Platform trials may provide a solution. Platform trials are a type of randomized clinical trial that allow simultaneous comparison of multiple intervention groups against a single control group that serves as a common control based on a prespecified interim analysis plan. The platform trial design enables introduction of new interventions after the trial is initiated to evaluate multiple interventions in an ongoing manner using a single overarching protocol called a master (or core) protocol. When multiple treatment candidates are available, rapid scientific therapeutic discoveries may then be made [29].

NEC Prevention

While the discussion of NEC definitions or treatments is ongoing, in the end, prevention of NEC is the best option for preterm infants. In previous years we have put a lot of attention to human (donor) milk and probiotics. In the above articles, we discuss shortly new data on 2 other possible prophylactic interventions [30–32].

Oropharyngeal colostrum therapy reduces the incidence of ventilator-associated pneumonia in very low birth weight infants: a systematic review and meta-analysis

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Does oropharyngeal administration of colostrum reduce morbidity and mortality in very preterm infants? A randomised parallel-group controlled trial

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Efficacy and safety of enteral recombinant human insulin in preterm infants: a randomized clinical trial

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JAMA Pediatr 2022;176:452–460
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Comments: For oropharyngeal colostrum administration, the jury is still out there, but does not tend to be supportive. The most recent meta-analysis (8 RCTs, 682 patients) performed by Ma et al., published in 2021, showed borderline significance in favor of using oropharyngeal colostrum administration [30]. However, adding the Aggarwal et al. study from India (n = 260 infants) will probably not result in a significant reduction on the incidence of NEC or other morbidities [31]. In conclusion, while administration of oropharyngeal colostrum to preterm infants appears safe and theoretically attractive from both an emotional and immunological point of view, especially in high-resource settings, no clear clinical benefits have consistently been proven unfortunately.

Another study of interest discussed here by Mank et al. examined the effect of recombinant human (rh) insulin on feeding tolerance [32]. This multicenter, double-blind, placebo-controlled randomized clinical trial was conducted at 46 neonatal intensive care units throughout Europe, Israel, and the USA and included 303 preterm infants in total. Tolerance to enteral feeding improved which was defined as a significant reduction of time to full enteral feeding (median reduction of 4 days). Besides, also of interest, there seemed to be a reduction of NEC grades 2 and 3 in the rh-insulin-supplemented groups. As this was a secondary outcome and the study was not powered to detect a significant difference, these results can only be considered as hypothesis generating. Another large RCT on rh-insulin is planned, so we will have to await those results, to see whether this may truly form another prophylactic treatment for NEC prevention in preterm infants.

Term Infants

Breastfeeding

Breastfeeding is the optimal feeding for infants. We discuss below 2 papers on breastfeeding and health benefits and 1 on osteopathic manipulative treatment (OMT) and improvement of breastfeeding [33–35].

Associations of breastfeeding with childhood autoimmunity, allergies, and overweight: The Environmental Determinants of Diabetes in the Young (TEDDY) study

Hummel S[1], Weiß A[1], Bonifacio E[2], Agardh D[3], Akolkar B[4], Aronsson CA[3], Hagopian WA[5], Koletzko S[6,7], Krischer JP[8], Lernmark Å, Lynch K[8], Norris JM[9], Rewers MJ[10], She JX[11], Toppari J[12,13], Uusitalo U[8], Vehik K[8], Virtanen SM[14,15,16,17], Beyerlein A[1], Ziegler AG[1], TEDDY Study Group

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Breastfeeding and risk of overweight in childhood and beyond: a systematic review with emphasis on sibling-pair and intervention studies

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Osteopathic manipulative treatment to improve exclusive breast feeding at 1 month

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Arch Dis Child Fetal Neonatal Ed 2021;106:F591–F595

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Comments: The impact of breastfeeding remains questioned on various long-term health outcomes such as cardiometabolic health. Since it is unethical to randomly assign children into breastfeeding and non-breastfeeding treatment groups, observational studies are performed to assess the association between breastfeeding and long-term health outcomes. Information on infant feeding is often collected retrospectively because it is rare to have a large cohort study to collect data at multiple time points during infancy to capture breastfeeding information prospectively. The TEDDY study is a large birth cohort study prospectively following children with increased genetic susceptibility for type 1 diabetes and celiac disease in Finland, Germany, Sweden, and the United States for the development of islet and transglutaminase autoantibodies. It collects prospective information on environmental exposures and childhood conditions, such as allergy, as well as demographic and anthropometric data, such as type and feeding and growth. Hummel et al. used information from the TEDDY cohort to investigate whether breastfeeding is associated with the development of 3 health outcomes: autoimmunity, allergy, and obesity [33].

A total of 8,676 infants were followed for the development of autoantibodies to islet autoantigens or transglutaminase, allergies, and for anthropometric measurements up to a median age of 8.3 years. Information on breastfeeding was collected at 3 months of age and prospectively thereafter. The risk of obesity was assessed at 5.5 years of age. Breastfeeding duration was not associated with a lower risk of either islet or transglutaminase autoimmunity. Exclusive breastfeeding >3 months was associated with a decreased risk of seasonal allergic rhinitis (adjusted HR: 0.70; 95% CI: 0.53, 0.92; $p < 0.01$). Any breastfeeding >6 months and exclusive breastfeeding >3 months were associated with decreased risk of obesity (adjusted OR: 0.62; 95% CI: 0.47, 0.81; $p < 0.001$; and adjusted OR: 0.68; 95% CI: 0.47, 0.95; $p < 0.05$, respectively).

Of note, the TEDDY study population was selected based on the presence of a human leukocyte antigen genotype conferring risk of type 1 diabetes. Therefore, the results on autoimmunity and seasonal allergic rhinitis outcomes may not be generalizable to the general population.

The relationship between breastfeeding and reduction of the risk for overweight and obesity later in life is controversial. Early evidence from observational studies suggested that breastfeeding was associated with a slightly lower mean BMI than was formula feeding [36], but the randomized breastfeeding promotion intervention trial from Belarus (PROBIT) did not show reduction in child obesity assessed at age 6.5 years [37]. Two reviews of, respectively, 40 systematic reviews and 28 systematic reviews and meta-analyses published in 2016 both demonstrated an association between breastfeeding and a modest reduction (the odds decreased by 13% based on high-quality studies) in the risk of later overweight and obesity in children [38, 39].

Given the observational nature of available studies, confounding could not be ruled out. Education, socioeconomic status, and race are associated with both initiation and duration of breastfeeding in high-income countries. Socioeconomic factors are also associated with BMI and/or overweight and obesity in early childhood.

In the development of the 2020–2025 Dietary Guidelines for Americans, another systematic review was conducted on the relation between breast milk consumption and subsequent overweight and obesity. This review included 42 articles from 31 individual studies, primarily observational, with a focus on healthy full-term infants [40]. To address the issue of confounding, Dewey et al. have synthesized the results from the above-mentioned systematic review with emphasis on the 6 cohorts with sibling-pair analysis and the PROBIT study. The advantage of sibling-pair studies is that they should reduce confounding due to genetics, parenting practices, and environmental characteristics.

Moderate evidence suggested that "ever," compared with "never," consuming breast milk is associated with a lower risk of overweight and obesity at ages 2 years and older, particularly if the duration of breast milk consumption is >6 months. However, residual confounding could not be ruled out. Evidence was insufficient to determine the relation between the duration of any human milk consumption and overweight and/or obesity at age 2 years and older. This was based on the inconsistency in the findings.

Further research is needed to better understand the relationship between infant feeding practices and the risk of overweight or obesity in later life, as well as the biological and behavioral mechanisms if the relation is causal.

The use of OMT in pediatrics is very limited due to the lack of evidence with respect to safety and efficacy. A systematic, scoping review of pediatric osteopathic medicine published in 2021 yielded 315 unique articles. It was concluded that there is little strong, scientific, evidence-based literature demonstrating the therapeutic benefit of OMT for pediatric care [41]. Among breastfeeding-support programs, OMT is a frequently used approach, although with no evidence of efficacy. Jouhier et al. hypothesized that OMT, when added to medical support, would improve rates of exclusive breastfeeding at 1 month of age [35]. Breastfed term infants recruited at the University Hospital of Nantes, France were eligible if one of the following criteria was met: suboptimal breastfeeding behavior, maternal cracked nipples, or maternal pain. The infants were randomly assigned to the intervention or the control group. The intervention consisted of 2 sessions of early OMT, while in the control group, the manipulations were performed on a doll behind a screen. A total of 128 mother-infant dyads were randomized, with 64 assigned to each group. There was no statistical difference in the rate of breastfeeding at the age of 1 month between the 2 groups, and no adverse effects were reported in either group. Jouhier et al. concluded that OMT did not have a significant effect on the rate of exclusive breastfeeding at 1 month and that there is insufficient evidence to recommend OMT for breastfeeding support.

Breast Milk Substitutes

We discuss 3 papers on breast milk substitutes [42–44].

Conduct and reporting of formula milk trials: systematic reviews

Helfer B[1,2], Leonardi-Bee J[3], Mundell A[4], Parr C[1], Ierodiakonou D[5], Garcia-Larsen V[1,6], Kroeger CM[7], Dai Z[7,8], Man A[1], Jobson J[1], Dewji F[1], Kunc M[1], Bero L[9], Boyle RJ[1,10]

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BMJ 2021;375:n2202

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https://pubmed.ncbi.nlm.nih.gov/34645600/

Lactoferrin reduces the risk of respiratory tract infections: a meta-analysis of randomized controlled trials

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Clin Nutr ESPEN 2021;45:26–32

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https://pubmed.ncbi.nlm.nih.gov/34620326/

Infant formulas with postbiotics: an updated systematic review

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J Pediatr Gastroenterol Nutr 2022;74:823–839

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Comments: Helfer et al. conducted a systematic review to evaluate the conduct and reporting of formula milk trials. They had a special interest in understanding the risk of bias in published formula trials and if trial procedures could cause harm by undermining breastfeeding of participants [42].

A total of 307 trials published between 2006 and 2020 were identified, of which only 73 (24%) trials in 13,197 children were prospectively registered. Another 111 unpublished but registered trials in 17,411 children were identified. Detailed analysis was undertaken for 125 trials (23,757 children) published since 2015. Only 17 (14%) of these trials were conducted independently of breast milk substitute companies, 26 (21%) were prospectively registered with a clear aim and primary outcome, and authors or sponsors shared prospective protocols for 11 (9%) trials. Risk of bias was low in only 5 (4%) and high in 100 (80%) recently published trials, mainly because of inappropriate exclusions from analysis and selective reporting. Primary outcomes were reported by authors as favorable in 86 (69%) trials, and 115 (92%) abstract conclusions were favorable. One of 38 (3%) trials in partially breastfed infants reported adequate support for breastfeeding, and 14 of 87 (16%) trials in non-breastfed infants confirmed the decision not to breastfeed was firmly established before enrolment in the trial. In most recent trials, investigators were employed by, or had financial links to, the industry, who were often involved in the statistical analysis and writing. There is a lack of transparency of clinical trials, and evidence of selective reporting between and within trials.

Lactoferrin is a multifunctional protein of the transferrin family. Lactoferrin can be purified from milk or produced recombinantly. Human colostrum has the highest concentration, followed by mature breast milk, then cow's milk. Lactoferrin from breast milk has a bacteriostatic activity against *Escherichia coli*, and was also found to be able to kill pathogens, such as *Vibrio cholera* and *Streptococcus mutans*. Lactoferrin also can affect and modulate immune function in the infant, thereby affecting health outcomes. Human and bovine lactoferrin are analogous with respect to structure and function; about 78% of the human lactoferrin sequence is similar to the bovine lactoferrin. Various studies have demonstrated its protective role against respiratory tract infections (RTIs). Ali et al. performed a meta-analysis [43] to elucidate the association of lactotransferrin supplementation to infant formula in reducing the risk of RTIs by systematically reviewing the data from RCTs.

The primary outcome was a reduction in respiratory illness and decrease in frequency, symptoms, and duration. A total of 9 RCTs were eligible for this review, of which 6 were included in the meta-analysis. Two studies demonstrated a high risk of bias. The meta-analysis revealed a significantly reduced odds of developing RTIs with the use of lactotransferrin relative to the control (pooled odds ratio 0.57; 95% confidence interval 0.44–0.74, $n = 1,194$). Of note, the findings of this meta-analysis are limited by undersized cohorts and substantial risk of biases in few studies. Very well-designed RCTs are needed to warrant the routine use of lactotransferrin in infant formula.

The term postbiotic appropriately refers to substances derived after the microorganisms are no longer alive. The microbes comprising a postbiotic may be inanimate, intact cells or may be structural fragments of microbes, such as cell walls. Many preparations of postbiotics also retain microbe-produced substances, such as metabolites, proteins, or peptides, which may contribute to the overall health effect conferred by a postbiotic. Postbiotics are also known as fermented formulas, that is, those fermented with lactic acid–producing bacteria during the production process and not containing significant amounts of viable bacteria in the final product. Infant formulas supplemented with postbiotics are available in a growing number of countries worldwide. They are more expensive than regular infant formulas and often bear claims, including health claims the substantiation of which may not be supported by strong scientific data.

Szajewska et al. report an update of their 2015 systematic review on infant formula with postbiotics [44]. They assessed safety and clinical effects of the consumption of

infant formula with probiotics (with or without the addition of other ingredients) compared with standard infant formula. Eleven RCTs were included in the systematic review. Five trials had an overall high risk of bias, and 6 trials had some concerns of bias. Most data were available on infant formula fermented with Bifidobacterium breve C50 and *Streptococcus thermophilus* (BB/ST). These infant formulas were safe and well tolerated. Postbiotic infant formulas with additional modifications (i.e., infant formulas fermented with BB/ST and prebiotics, partly fermented infant formulas with BB/ST and prebiotics with or without modified milk fat, partly fermented antiregurgitation infant formulas with BB/ST and prebiotics) were safe and well tolerated but did not offer clear benefits replicated in other studies.

Several trials have evaluated the gut microbiota and documented that the administration of a postbiotic infant formula results in gut microbiota closer to that in breastfed infants. However, direct causal links between the gut microbiota and health outcomes have not been well established. Overall, the findings from published trials evaluated in this review provide reassurance that infant formulas supplemented with postbiotics are safe and well tolerated by infants who cannot be breastfed. However, their use was not associated with any health benefits.

Food Allergy

The prevalence of allergic reactions to foods is increasing, especially in high-income countries, where up to 10% of the population experience food allergy (FA). However, geographical variability in the incidence, type, and clinical presentation of FA as well as variations in symptoms and clinical phenotypes due to age, ethnicity, and other allergic diseases exists. We discuss below 2 papers on this topic [45, 46].

Food allergy across the globe

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Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial

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Lancet 2022;399:2398–2411

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Comments: The aim of the review article from many well-known international experts in the field was to provide an overview of the incidence of FA, causes, prevention strategies, diagnostic methods, and recommendations for treatment in FA [45]. Studies in the USA found that 7.6% of children and 10.8% of adults had probable FA; in children with FA, 40% were affected by more than 1 FA. Birth cohorts from Europe showed a mean incidence at age 2 years of 1.23% for egg allergy, and 0.54% for cow's milk allergy. In Asia, South and Central America, and Africa, reliable epidemiological data are limited. The 2 most important risk factors for FA development early in life are delayed introduction of allergenic solid foods and skin barrier dysfunction. The dual allergen exposure hypothesis suggests that food allergen exposure through damaged skin before exposure through the alimentary tract might lead to the development of FA.

Findings from recent studies of early-life dietary interventions for FA prevention have led to revised guidelines, moving from an avoidance approach of allergenic foods to actively recommending introduction of allergenic foods in the first 4–6 months of life. There is no consistent evidence that breastfeeding is effective for the prevention of allergic disease. However, for optimal health of the infant, the WHO and the European Academy of Allergology and Clinical Immunology recommend exclusive breastfeeding for a duration of 6 months and 4 months, respectively. There is no evidence that hydrolyzed formula prevents atopic disease in infants, even in those at high risk for allergic disease. The European Academy of Allergology and Clinical Immunology guidelines also recommend against the use of regular cow's milk formula in the first week of life. Oral immunotherapy (OIT) is increasingly advocated by pediatric allergologists, and an OIT drug for peanut allergy, in children aged 4–17 years, has been approved by FDA and European Medicines Agency in 2020.

Evidence to support early introduction of food allergens before the age of 4 months in all infants from the general population irrespective of individual allergy risk is still a matter of debate since data are scarce. In addition, starting early introduction <6

months contradicts with the WHO recommendations, i.e., exclusive breastfeeding for the first 6 months of life and introduction of complementary foods thereafter.

Atopic dermatitis, a common chronic inflammatory skin disease associated with reduced skin barrier function, is a strong risk factor for subsequent FA. Combining dietary modifications and improved skin barrier function in early infancy to prevent FA has therefore been suggested. The PreventADALL (Preventing Atopic Dermatitis and ALLergies in children) study is the first large, population-based RCT combining the early introduction of food allergens and regular emollients aiming to prevent atopic dermatitis or FA in children. In this study, Skjerven et al. aimed at determining whether early food or skin interventions prevented FA at age 36 months [46]. This cluster-randomized trial was performed at Oslo University Hospital and Østfold Hospital Trust, Oslo, and Karolinska University Hospital, Stockholm. Infants of women recruited antenatally at the routine 18-week ultrasound examination were cluster-randomized at birth to the following groups: (1) no intervention group; (2) the skin intervention group (skin emollients; bath additives and facial cream; from age 2 weeks to <9 months, both at least 4 times per week); (3) the food intervention group (early CF of peanut, cow's milk, wheat, and egg from age 3 months); or (4) the combined intervention group (skin and food interventions). The primary outcome was allergy to any interventional food at 36 months of age. A total of 2,697 women with 2,701 pregnancies were recruited, from whom 2,397 newborn infants were enrolled. FA was diagnosed in 44 children; 14 (2.3%) of 596 infants in the non-intervention group, 17 (3.0%) of 574 infants in the skin intervention group, 6 (0.9%) of 641 infants in the food intervention group, and 7 (1.2%) of 583 infants in the combined intervention group. Peanut allergy was diagnosed in 32 children, egg allergy in 12 children, and milk allergy in 4 children. Prevalence of FA was reduced in the food intervention group compared with the no intervention group (risk difference −1.6% [95% CI −2.7 to −0.5]; odds ratio [OR] 0.4 [95% CI 0.2 to 0.8]), but not compared with the skin intervention group (0.4% [95% CI −0.6 to 1.5%]; OR 1.3 [0.7 to 2.3]). The overall protective effect of the intervention was driven by the peanut allergy results: 23 (2.0%) of 1,170 infants in the no food intervention groups had peanut allergy compared with 9 (0.7%) of 1,224 infants in the food intervention groups, i.e., a 63% reduction. The proportion of infants with egg allergy at 3 years was low in both groups (7 [0.6%] of 1,170 infants in the no food intervention groups; 5 [0.4%] of 1,224 infants in the food intervention groups). No serious adverse events were observed. Since families were not asked to record the actual amount of allergenic foods consumed, there is residual uncertainty regarding the dose of food required to induce tolerance. The results of this well-designed study demonstrate that early introduction of common allergenic foods from 3 months of age is a safe and effective strategy to prevent FA in all infants, including those not at risk of FA in whom most cases of FA occur.

Complementary Feeding

The CF period is a developmental interval during which young children not only receive new foods, but also learn about flavors, food, and eating. Although evidence is limited regarding how the order of food group introduction relates to later food acceptance and dietary diversity, dietary recommendations for infants and toddlers include consumption of foods from all food groups. The long-term consequences of the CF pattern and the nature and of complementary foods are also poorly known. We discuss below 2 RCTs on CF [47, 48].

Effect of a healthy eating intervention in the first months of life on ultraprocessed food consumption at the age of 4–7 years: a randomised clinical trial with adolescent mothers and their infants

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Br J Nutr 2021;126:1048–1055

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Starting complementary feeding with vegetables only increases vegetable acceptance at 9 months: a randomized controlled trial

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Am J Clin Nutr 2022;116:111–121

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Comments: Ultraprocessed foods (UPF) are industrial formulations of substances derived from foods with little or no whole food and often containing added colorings, flavorings, emulsifiers, thickeners, and other cosmetic additives to make them palatable. UPF negatively impacts the quality of the diet with a high content in energy, saturated and *trans* fats, sodium, and a low content in fiber and micronutrients. In the adult and elderly population, there is increasing evidence on the association of UPF consumption with the development of noncommunicable diseases such as obesity, type 2 diabe-

tes, cardiovascular disease, cancer, depression, gastrointestinal disorders, mortality from all causes, and risk of cardiometabolic diseases. There is also consensus that a healthy diet in early life, including exclusive breastfeeding up to 6 months and complemented breastfeeding up to 2 years or more, is key to establishing healthy eating habits. On the other hand, adolescent motherhood can negatively affect breastfeeding initiation and duration, as well as prompt the consumption of unhealthy foods in early life. Lazzeri et al. aimed at evaluating the impact of an educational intervention to promote breastfeeding and healthy CF in young infants of adolescent mothers, on the consumption of UPF at the age of 4–7 years [47]. A total of 323 teenage mothers and their infants from South Brazil were enrolled, 163 were allocated to the intervention group and 160 to the control group. Intervention consisted of sessions on breastfeeding and healthy CF promotion and was carried out in the maternity ward and at home after delivery. Food consumption was assessed at child's age of 4–7 years. The intervention reduced the risk of high consumption of UPF by 35% (relative risk: 0.65, 95% CI 0.43, 0.98).

Vegetables are an important part of the diet as they provide nutrients needed for growth, development, and overall health. In the United States, children's consumption of fruit but not vegetables has increased [49], and the Feeding Infants and Toddlers Study showed that consumption of dark green vegetables is particularly low among infants [50]. Reasons for poor vegetable intake range from infant preferences for sweet/energy-dense foods to simple lack of access, maternal dislike, or cultural practices.

Rapson et al. aimed to test whether exposure to vegetables only during the first 4 weeks of CF increases later vegetable acceptance compared with a control group receiving fruit and vegetables [48]. In this RCT, 117 infants from Auckland, New Zealand, received either vegetables only or a combination of fruit and vegetables for a duration of 4 weeks, starting from the first day of CF at around 4–6 months of age. The veg-only infants consumed more target vegetables (broccoli and spinach) than controls (mean difference [95% CI]: 11.83 [0.82, 22.84] g, $p = 0.036$ and 10.19 [0.50, 19.87] g, $p = 0.039$, respectively). Also, veg-only infants consumed more vegetables as a whole than controls (86.3 [52.5, 146.3] compared with 67.5 [37.5, 101.3] g, respectively, $p = 0.042$). Introducing vegetables as the first food was not associated with 9-month iron status. Rapson et al. concluded that providing vegetables as first foods increased vegetable intake at 9 months of age and may be an effective strategy for improving child vegetable consumption and developing preferences for vegetables in infancy.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 114–127 (DOI: 10.1159/000527939)

Cognition

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Introduction

It is widely documented that neurodevelopment is influenced by genetic and environmental factors. Environmental factors, mainly represented by lifestyle, are modifiable contributors to neurodevelopment. Modifiable factors include dietary patterns, whole foods (e.g., human milk), and intakes of specific nutrients from infancy to childhood. Accordingly, even the periconceptional period and pregnancy represent sensitive phases that should be monitored to optimize offspring's brain growth and cognitive functions.

This chapter includes a selection of studies performed in the area of nutrition and cognition, published between July 1, 2021 and June 30, 2022. Original articles comprising randomized controlled trials (RCTs), observational studies, and reviews have been selected and grouped into 4 categories, respectively:

1. Dietary patterns
2. Micronutrients
3. LC-PUFA (long-chain polyunsaturated fatty acid)
4. Toxicity

Key articles reviewed for this chapter

Dietary Patterns

Association of maternal dietary patterns during gestation and offspring neurodevelopment
Lv S, Qin R, Jiang Y, Lv H, Lu Q, Tao S, Huang L, Liu C, Xu X, Wang Q, Li M, Li Z, Ding Y, Song C, Jiang T, Ma H, Jin G, Xia Y, Wang Z, Geng S, Du J, Lin Y, Hu Z
Nutrients 2022;14:730

Association between dietary patterns and cognitive ability in Chinese children aged 10–15 years: evidence from the 2010 China family panel studies
Wang T, Cao S, Li D, Chen F, Jiang Q, Zeng
BMC Public Health 2021;21:2212

Maternal diet quality during pregnancy and child cognition and behavior in a US cohort
Mahmassani HA, Switkowski KM, Scott TM, Johnson EJ, Rifas-Shiman SL, Oken E, Jacques PF
Am J Clin Nutr 2022;115:128–141

Micronutrients

Benefits and risks of iron interventions in infants in rural Bangladesh
Pasricha SR, Hasan MI, Braat S, Larson LM, Tipu SMM-U, Hossain SJ, Shiraji S, Baldi A, Bhuiyan MSA, Tofail F, Fisher J, Grantham-McGregor S, Simpson JA, Hamadani JD, Biggs BA
N Engl J Med 2021;385:982–995

Effects of iron intake on neurobehavioural outcomes in African children: a systematic review and meta-analysis of randomised controlled trials
Mutua AM, Mwangi K, Abubakar A, Atkinson SH
Wellcome Open Res 2021;6:181

Pre-conceptional maternal vitamin B12 supplementation improves offspring neurodevelopment at 2 years of age: PRIYA trial
D'souza N, Behere RV, Patni B, Deshpande M, Bhat D, Bhalerao A, Sonawane S, Shah R, Ladkat R, Yajnik P, Bandyopadhyay SK, Kumaran K, Fall C, Yajnik CS
Front Pediatr 2021;9:755977

Maternal iodine intake and neurodevelopment of offspring: the Japan environment and children's study
Hisada A, Takatani R, Yamamoto M, Nakaoka H, Sakurai K, Mori C, and The Japan Environment and Children's Study Jecs Group
Nutrients 2022;14:1826

Folic acid intervention during pregnancy alters DNA methylation, affecting neural target genes through two distinct mechanisms
Ondičová M, Irwin RE, Thursby SJ, Hilman L, Caffrey A, Cassidy T, McLaughlin M, Lees-Murdock DJ, Ward M, Murphy M, Lamers Y, Pentieva K, McNulty H, Walsh CP
Clin Epigenetics 2022;14:63

LC-PUFA

Prenatal docosahexaenoic acid effect on maternal-infant DHA-equilibrium and fetal neurodevelopment: a randomized clinical trial

Gustafson KM, Christifano DN, Hoyer D, Schmidt A, Carlson SE, Colombo J, Mathis NB, Sands SA, Chollet-Hinton L, Brown AR, Mudaranthakam DP, Gajewski BJ

Pediatr Res 2022;92:255–264

Omega-3 fatty acid dietary supplements consumed during pregnancy and lactation and child neurodevelopment: a systematic review

Nevins JEH, Donovan SM, Snetselaar L, Dewey KG, Novotny R, Stang J, Taveras EM, Kleinman RE, Bailey RL, Raghavan R, Scinto-Madonich SR, Venkatramanan S, Butera G, Terry N, Altman J, Adler M, Obbagy JE, Stoody EE, de Jesus J

J Nutr 2021;151:3483–3494

Low linoleic acid foods with added DHA given to Malawian children with severe acute malnutrition improve cognition: a randomized, triple-blinded, controlled clinical trial

Stephenson K, Callaghan-Gillespie M, Maleta K, Nkhoma M, George M, Park HG, Lee R, Humphries-Cuff I, Lacombe RJS, Wegner DR, Canfield RL, Brenna JT, Manary MJ

Am J Clin Nutr 2022;115:1322–1333

Toxicity

The benefits of fish intake: results concerning prenatal mercury exposure and child outcomes from the ALSPAC prebirth cohort

Golding J, Taylor C, Iles-Caven Y, Gregory S

Neurotoxicology 2022;91:22–30

Impact of dietary mercury intake during pregnancy on the health of neonates and children: a systematic review

Saavedra S, Fernández-Recamales Á, Sayago A, Cervera-Barajas A, González-Domínguez R, Gonzalez-Sanz JD

Nutr Rev 2022;80:317–328

Interaction of prenatal bisphenols, maternal nutrients, and toxic metal exposures on neurodevelopment of 2-year-olds in the APrON cohort

Liu J, Martin LJ, Dinu I, Field CJ, Dewey D, Martin JW

Environ Int 2021;155:106601

Association of maternal dietary patterns during gestation and offspring neurodevelopment

Lv S[1,2], Qin R[1,3], Jiang Y[1,3], Lv H[1,3,4], Lu Q[1,5], Tao S,[1,3] Huang L[1,5], Liu C[1,3], Xu X[1,5], Wang Q[1], Li M[1,6], Li Z[1,6], Ding Y[5], Song C[3], Jiang T[7], Ma H[1,3,4], Jin G[1,3], Xia Y[1,6], Wang Z[5], Geng S[2], Du J[1,3,4], Lin Y[1,4,5], Hu Z[1,3,4]

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Nutrients 2022;14:730

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https://pubmed.ncbi.nlm.nih.gov/35215380/

Comments: The present prospective Jiangsu Birth Cohort (JBC) study investigated the role of maternal diet at different gestational weeks on neurodevelopment in children at 1 year of age. The authors included a total of 1,178 mother-infant pairs and have reported that a higher adherence score of "aquatic products, fresh vegetables, and homemade" food consumption in the second and third trimester was significantly associated with a decreased risk of nonoptimal cognitive development of infants.

Association between dietary patterns and cognitive ability in Chinese children aged 10–15 years: evidence from the 2010 China family panel studies

Wang T[1,2,3], Cao S[2], Li D[2], Chen F[2], Jiang Q[2], Zeng[1]

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BMC Public Health 2021;21:2212

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https://pubmed.ncbi.nlm.nih.gov/34863128/

Comments: This cross-sectional study investigated the association between 3 dietary patterns ("high protein," "high fat," and "high salt-oil") and cognitive ability in 2,029 Chinese children aged 10–15 years from the China Family Panel Studies. The results showed a positive relationship between "high protein" dietary patterns and mathematics and vocabulary test scores. In contrast, children with higher score of "high fat" dietary pattern were associated with poorer cognitive ability.

Maternal diet quality during pregnancy and child cognition and behavior in a US cohort

Mahmassani HA[1,2], Switkowski KM[3], Scott TM[1], Johnson EJ[1], Rifas-Shiman SL[3], Oken E[3,4], Jacques PF[1,2]

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Am J Clin Nutr 2022;115:128–141
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Comments: The authors selected 1,580 mother-child pairs from an ongoing prospective prebirth cohort study (Project Viva). Children completed ≥1 cognitive/behavioral assessment at infancy, early childhood, or midchildhood, and mothers completed the early- and/or midpregnancy study visits. Results showed that higher maternal MDS-P, a version of the Mediterranean diet score (MDS) modified for pregnancy, scores during pregnancy were associated with better verbal and nonverbal intelligence quotient scores and fewer metacognition problems in midchildhood. Higher maternal Alternate Healthy Eating Index scores, modified in occasion of pregnancy, were associated with better visual spatial skills in early childhood and with better verbal intelligence and executive function in midchildhood.

General Comments: Given the recognized influence of nutrition on cognitive and behavioral development in early life, the association between maternal food habits and child cognition deserves further investigation to optimize, not only single nutrient intakes, but the entire maternal dietary patterns during gestation. An extension of these studies back to the periconceptional period warrants further investigations, to disentangle a possible role also on the rate of fertility, to ameliorate the outcome of this more frequent, year-by-year, practice.

Micronutrients

Benefits and risks of iron interventions in infants in rural Bangladesh

Pasricha SR[1,2,3,4], Hasan MI[9], Braat S[1,5,6], Larson LM[1,5,10], Tipu SMM-U[9], Hossain SJ[9], Shiraji S[9], Baldi A[1,4], Bhuiyan MSA[9], Tofail F[9], Fisher J[8], Grantham-McGregor S[11], Simpson JA[6], Hamadani JD[9], Biggs BA[5,7]

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N Engl J Med 2021;385:982–995
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Comments: This double-blind, randomized, placebo-controlled trial aimed to assess the immediate and medium-term benefits and risks of daily supplementation in 8-month-old rural Bangladesh children. The authors included 3,300 infants, randomly assigned to receive iron syrup (first arm), iron-containing multiple micronutrient powders (second arm), or placebo, every day for 3 months. The sample size has been calculated to reach 80% power. The authors found no apparent effect of supplementations on child cognitive composite scores as compared to placebo. Neither iron syrup nor multiple micronutrient powders improved motor or language development, child behavior, or temperament, either immediately after completion of the assigned regimen or at 9 months after completion.

Effects of iron intake on neurobehavioural outcomes in African children: a systematic review and meta-analysis of randomised controlled trials

Mutua AM[1], Mwangi K[1], Abubakar A[1,2,3,4], Atkinson SH[1,5,6]

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Wellcome Open Res 2021;6:181
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https://pubmed.ncbi.nlm.nih.gov/35106382/

Comments: The investigators performed a systematic review and meta-analysis including 35 RCTs of which only 5 studies regarding 258 African children, whose range of age was 18 months up to 14 years. The authors found poor and heterogeneous evidence for the effects of iron supplementation or fortification on neurobehavioural outcomes. Once more, further well-designed studies should be performed on the developmental effects of nutritional interventions in African populations, with translational value as an approach to most developing and/or transition countries. A possible reason of discrepancies in results from narrative and/or systematic reviews may mainly depend on differences at baseline conditions among populations and groups that have been investigated as well as differences in study designs and nutritional interventions.

Pre-conceptional maternal vitamin B12 supplementation improves offspring neurodevelopment at 2 years of age: PRIYA trial

D'souza N[1], Behere RV[1], Patni B[2], Deshpande M[2], Bhat D[1], Bhalerao A[1], Sonawane S[1], Shah R[1], Ladkat R[1], Yajnik P[1], Bandyopadhyay SK[3], Kumaran K[4], Fall C[4], Yajnik CS[1]

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Front Pediatr 2021;9:755977

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Comments: Within the Pune Rural Intervention in Young Adolescents (PRIYA) trial, this study aimed to evaluate the role of maternal preconceptional B12 and micronutrient supplementation (starting at 17 years) on offspring neurodevelopmental performance at 24–42 months of age, in India. The enrolment included 266 adolescent females, randomized to receive either a placebo (first arm), B12 plus multiple micronutrients (second arm), or B12 alone (third arm), from preconception stage until delivery. Intervention groups were provided with vitamin B12 (2 µg/day) with or without multiple micronutrients. Among enrolled women, 149 delivered a live baby. After 2 years the parents of 85 children have been approached for the cognitive assessment, that has been stopped on February 2020, due to the COVID-19 pandemic, and the final analysis was based on 74 children. The supplementation of adolescents with 2 µg/day of B12 significantly improved their own B12 status (total B12 and holo-transcobalamin, TC) and offspring cord blood holo-TC, with a positive impact on the cognitive development of their children at 2 years of age.

Maternal iodine intake and neurodevelopment of offspring: the Japan environment and children's study

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Nutrients 2022;14:1826

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https://pubmed.ncbi.nlm.nih.gov/35565793/

Comments: This study was based on the Japan Environment and Children's Study (JECS), a prospective birth cohort, and investigated maternal iodine intake during gestation on neurodevelopmental delay in their children. In total, 75,249 and 66,604 mother-child pairs with children aged 1 and 3 years, respectively, were enrolled for analysis. The authors found out that low iodine intake levels in pregnancy increased the risk of delay in child neurodevelopment at 1 and 3 years of age, and the number of pregnant women with poor iodine status was almost widespread.

Folic acid intervention during pregnancy alters DNA methylation, affecting neural target genes through two distinct mechanisms

Ondičová M[1], Irwin RE[1], Thursby SJ[1,7], Hilman L[1], Caffrey A[2], Cassidy T[3], McLaughlin M[3], Lees-Murdock DJ[1], Ward M[2], Murphy M[4], Lamers Y[5], Pentieva K[2], McNulty H[2], Walsh CP[1,6]

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Clin Epigenetics 2022;14:63

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https://pubmed.ncbi.nlm.nih.gov/35578268/

Comments: The authors used samples from their previous RCT of folic acid (FA) supplementation in either the second and third trimester, where significant improvements of cognition have been demonstrated in children from mothers supplemented with FA during pregnancy. Genes showing significant differences were identified using pyrosequencing and mechanistic approaches. Continued FA supplementation of pregnant mothers in the second and third trimester of pregnancy led to genome-wide hypomethylation in the cord blood of their offspring. Tissue-specific gene ontology analysis and analysis of top-ranking regions highlighted a strong association with neurodevelopmental steps. The results further support evidence for a continued supplementation FA throughout later gestation, even beyond the time limit suggested for the prevention of neural tube defects.

General Comments: We have presented a selection of studies on micronutrient intakes during preconceptional, pregnancy, and first phases of life in developing and developed countries, and their associations with neural performances. It is widely agreed that ensuring adequate maternal micronutrient intake, in particular, iron, vitamin B12, iodine, and folic, is mandatory to optimize early-life neurodevelopment. Uncertainty still remains, after years of intensive and extensive research on the association between dietary supplementations of iron and FA in pregnancy, respectively, on neurodevelopmental scores later on. According to previous intervention studies and observations, available evidence suggests that (1) iron supplementation has positive effects when the iron-deficiency anemia is clinically suggestive and confirmed by blood biochemistry, and (2) when the supplementation with FA, even if protracted, is maintained within recommended dosages [1, 2]. Based on these observations, newer well-designed studies in developing countries are required to better understand the effects and needs in settings where poor nutrition is common.

Prenatal docosahexaenoic acid effect on maternal-infant DHA-equilibrium and fetal neurodevelopment: a randomized clinical trial

Gustafson KM[1,2], Christifano DN[2,3], Hoyer D[4], Schmidt A[4,5], Carlson SE[3], Colombo J[6], Mathis NB[2], Sands SA[3], Chollet-Hinton L[7], Brown AR[7], Mudaranthakam DP[7], Gajewski BJ[7]

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Pediatr Res 2022;92:255–264

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https://pubmed.ncbi.nlm.nih.gov/34552200/

Comments: This randomized, longitudinal, double-blind, single-center trial, conducted at the University of Kansas Medical Center (USA), aimed to examine the rate of maternal-infant docosahexaenoic acid (DHA) equilibrium at delivery and its effect on fetal heart rate variability (HRV) score and fetal autonomic brain age score (fABAS) at 32 and 36 weeks gestation. Three hundred pregnant women have been randomly supplemented with 200 or 800 mg of DHA during pregnancy until delivery and blood samples of 262 maternal-infant dyads have been collected at delivery. Power computations have indicated that 125 participants per group may provide 88% power. Participants who received a higher dose of DHA were more likely to achieve maternal-infant DHA equilibrium at delivery. Moreover, there is a lower threshold of maternal DHA status where maternal-infant DHA equilibrium never occurs. However, within this sample, the equilibrium status was not related to fetal neurodevelopment.

Omega-3 fatty acid dietary supplements consumed during pregnancy and lactation and child neurodevelopment: a systematic review

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J Nutr 2021;151:3483–3494
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Comments: The authors performed a systematic review to evaluate the impacts of omega-3 fatty acid supplementation before and during pregnancy and lactation on cognitive development in children. Finally, 33 articles have been included. According to their conclusions, omega-3 fatty acid supplementation during pregnancy may be beneficial for neurodevelopment in children. However, there was insufficient and heterogeneous evidence to make a specific recommendation about routine supplementation with omega-3 fatty acids before and during pregnancy and breastfeeding.

Low linoleic acid foods with added DHA given to Malawian children with severe acute malnutrition improve cognition: a randomized, triple-blinded, controlled clinical trial

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Am J Clin Nutr 2022;115:1322–1333
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Comments: This triple-blind, randomized, controlled clinical trial compared neurocognitive function in 2,565 Malawian children with uncomplicated severe acute malnutrition, age range 6–59 months, treated with 3 different ready-to-use therapeutic food (RUTF): RUTF made with reduced amounts of linoleic acid (LA) without added DHA (HORUTF), first arm; added DHA (DHA-HORUTF), second arm; and standard RUTF (SRUTF, third arm). The results showed that DHA-HORUTF achieved superior global Malawi Developmental Assessment Tool (MDAT) z-scores than children who consumed SRUTF. This study provides the first direct evidence that reduction in LA and addition of DHA in RUTF enhances cognition in children with severe acute malnutrition.

General Comments: We have selected 3 studies with heterogeneous results. Indeed, in the first RCT, maternal DHA equilibrium status was not related to fetal neurodevelopment, while the other 2 studies may support that omega-3 supplementation during gestation and childhood may positively influence brain development and cognitive function. Waiting for larger trials, we may consider the various individual polymorphisms of indi-

vidual fatty acids, to explain the differences of results according to genetics. Nevertheless, nonnegative results have been found in association with LC-PUFA supplementations in terms of cognitive achievement. On the whole, the results from these investigations and other studies suggest to reconsider the effects of the whole pattern of FA, not limited to longer-chain PUFA, considering the peculiar, favorable observations at long term of breastfeeding and human milk composition, inclusive of the whole FA pattern, on developmental scores.

Toxicity

The benefits of fish intake: results concerning prenatal mercury exposure and child outcomes from the ALSPAC prebirth cohort

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Neurotoxicology 2022;91:22–30
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Comments: This review used data collected by the Avon Longitudinal Study of Parents and Children (ALSPAC) [3, 4], in a relatively industrialized area in south-west of England, to assess the influence of maternal consumption of mercury-containing foods during pregnancy on child cognitive development. The investigators have summarized the results of 12 papers that have used data from the ALSPAC. Estimates of fetal mercury exposures have been compared with various cognitive outcomes measured during the child's development, such as preschool cognition assessment (vocabulary, social activity), school-age cognition assessment (IQ full-scale, IQ verbal, IQ performance), and 6 measures of behavior. Positive and significant associations with prenatal mercury levels were shown for total and performance IQ, mathematical/scientific reasoning, and birthweight in fish-consuming versus non-fish-consuming mothers. Seafood contains several dietary factors, first of all PUFAs, but also others, such as iodine and amino acids, that may contribute to neurodevelopment, beyond the potential negative effects of metal's contamination.

Impact of dietary mercury intake during pregnancy on the health of neonates and children: a systematic review

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Nutr Rev 2022;80:317–328

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Comments: The investigators conducted a systematic review to examine the relationships between maternal exposure to methyl mercury with diet during gestation and the health of the offspring up to 8 years of age. It is widely agreed that maternal higher mercury levels during pregnancy relate to lower scores in various neuropsychological and developmental tests. Nevertheless, consistent with the findings from the ALSPAC study, mercury toxicity may be attenuated by other crucial nutrients in the maternal diet, such as PUFAs.

Interaction of prenatal bisphenols, maternal nutrients, and toxic metal exposures on neurodevelopment of 2-year-olds in the APrON cohort

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Environ Int 2021;155:106601

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Comments: The authors investigated 394 mother-child pairs to examine the total bisphenol-A (BPA) and bisphenol-S (BPS) concentrations metals and maternal nutrient status on child cognitive development at 2 years of age. All samples and data were extracted from mothers and children participating in the Alberta Pregnancy Outcomes and Nutrition (APrON) study. Results showed that only higher maternal exposure of cadmium, in particular from canned fish [5], was significantly associated with lower motor scores but it did not modify the relationships between bisphenols and neurodevelopment in the present cohort. Furthermore, maternal selenium status was a significant effect-measure modifier of the relationship between maternal bisphenols and child motor development, appearing protective against the adverse effects of bisphenols.

General Comments: Through many years observational studies have increasingly considered the effects of toxic element intake during pregnancy on child cognition. The main dietary sources of toxic elements are usually represented by water, rice grain and other cultivated grains, vegetables, chicken, soil, and marine organisms, especially fish and seafood, from coastal areas, associated with industrial discharge [6, 7].
On the other side, the role of whole foods and their dietary patterns as far neuroprotection should be considered too. Examples are represented by fish (as in the ALSPAC study) with its whole composition, compared with the potential negative effects of methyl mercury, as well as other examples of negative (such as cadmium) and positive (such as selenium) contributors in neuroprotection.

Overview

Within the yearly section on Nutrition and Neurodevelopment, the associations of single nutrients as well whole foods (fish as first) have been considered for their effects on neural functional outcomes, mostly starting from preconception and pregnancy. It seems that unavoidable heterogeneity (from populations to study designs) makes it difficult to draw definitive conclusions. Neurotoxicity associated with specific micronutrients, possibly counteracted by other nutrients and/or foods, is another emerging issue, as far as safety is concerned. In parallel, we see a growing general interest in sustainability, strictly associated to local dietary patterns [8]. In holistic perspective, the associations of single nutrients and/or foods with developmental achievements should therefore be considered within the context of local dietary patterns, and adjusted for these variables, to improve the quality of the approach and the translational value of the results.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 128–139 (DOI: 10.1159/000527947)

Nutrition and Chronic Diseases

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Introduction

The fascinating and complex process of growth and the changes in body composition are subjected to alternations when facing chronic diseases during childhood and adolescence. Many chronic diseases can potentially result in growth impairment, due to numerous co-existing contributing factors that include suboptimal nutrition, high energy needs, chronic inflammation, and hormonal imbalance.

Eight leading articles were selected and reviewed in this chapter, highlighting different aspects of growth and nutrition in 5 major chronic diseases of childhood: asthma, celiac disease, inflammatory bowel disease, cholestatic liver disease, and chronic kidney disease. We encourage the readers to explore the various topics discussed in this chapter, and to expand their knowledge in contemporary issues regarding pediatric chronic diseases and their interaction with the process of growth and nutritional status.

Key articles reviewed for this chapter

Asthma

Height and bone mineral content after inhaled corticosteroid use in the first 6 years of life
Kunøe A, Sevelsted A, Chawes BLK, Stokholm J, Krakauer M, Bønnelykke K, Bisgaard H
Thorax 2022;77:745–751

The influence of childhood asthma on adult height: evidence from the UK Biobank
Chen W, Yang H, Hou C, Sun Y, Shang Y, Zeng Y, Hu Y, Qu Y, Zhu J, Fang F, Lu D, Song H
BMC Med 2022;20:94

Celiac Disease

Evaluation of parameters associated with growth retardation in children with coeliac disease
Taskin DG, Sursal A, Dogan AE, Ozdener F
J Paediatr Child Health 2021;57:1454–1459

The effect of gluten-free diet on body mass index in paediatric celiac disease
Anafy A, Cohen S, Ben Tov A, Amir A, Weintraub Y, Moran-Lev H, Dali Levy M, Ankona Bussel M, Yerushalmy Feler A
Acta Paediatr 2021;110:2233–2239

Inflammatory Bowel Disease

Pediatric-onset inflammatory bowel disease has only a modest effect on final growth: a report from the epi-IIRN
Assa A, Assayag N, Balicer RD, Gabay H, Greenfeld S, Kariv R, Ledderman N, Matz E, Dotan I, Ledder O, Yerushalmy-Feler A, Turner D, Cohen S
J Pediatr Gastroenterol Nutr 2021;73:223–230

Moderate-to-vigorous physical activity is associated with higher bone mineral density in children with inflammatory bowel disease
Trivić I, Sila S, Batoš AT, Mišak Z, Kolaček S, Hojsak I
J Pediatr Gastroenterol Nutr 2022;74:54–59

Chronic Liver Disease

Body composition correlates with laboratory parameters and disease severity in infants with biliary atresia
Marderfeld L, Waisbourd-Zinman O, Biran N, Rozenfeld Bar-Lev M, Silbermintz A, Poraz I, Reznik D, Jack Y, Mozer Glassberg Y, Shamir R
Pediatr Transplant 2022;26:e14208

Chronic Kidney Disease

Incidence of and risk factors for short stature in children with chronic kidney disease: results from the KNOW-Ped CKD
Park E, Lee HJ, Choi HJ, Ahn YH, Han KH, Kim SH, Cho H, Shin JI, Lee JH, Park YS, Ha IS, Cho MH, Kang HG
Pediatr Nephrol 2021;36:2857–2864

Height and bone mineral content after inhaled corticosteroid use in the first 6 years of life

Kunøe A[1], Sevelsted A[1], Chawes BLK[1], Stokholm J[1,2], Krakauer M[3,4], Bønnelykke K[1], Bisgaard H[1]

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Thorax 2022;77:745–751

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The influence of childhood asthma on adult height: evidence from the UK Biobank

Chen W[1,2,3], Yang H[2,3], Hou C[2,3], Sun Y[2,3], Shang Y[2,3], Zeng Y[2,3], Hu Y[2,3], Qu Y[2,3], Zhu J[4], Fang F[5], Lu D[2,5,6], Song H[2,3,7]

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BMC Med 2022;20:94

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Comments: Long-term use of inhaled corticosteroids (ICS) is widely common and is the preferred treatment in childhood asthma. Although the safety profile of ICS is significantly more favorable than that of oral corticosteroids, there is still uncertainty regarding the potential for systemic complications including growth alternation and bone health in children on continuous treatment [1, 2]. Young children might be particularly vulnerable to growth impairment, both due to repetitive corticosteroid or continuous treatment, as well as the negative effect of the inflammatory process, in the midst of a period of rapid growth.

In the study discussed herewith by Kunøe et al. over 1,000 children with asthma were followed prospectively from birth to the age of 6 years, and the cumulative dose of ICS was analyzed. The patients' height *z*-score at 6 years of age was compared to the height/length *z*-score at 1 year, in 84% of the cohort. Dual-energy X-ray absorptiometry scans were performed at 6 years of age in 71% of the cohort. The results of this study demonstrated an inverse association between cumulative ICS use and height at 6 years. However, this finding was only significant among patients with continuous ICS exposure after the age of 5 years, which is 1 year prior to the height assessment, with a −0.31 cm (95% CI: −0.52 to −0.1) difference per year on standard treatment, *p*

< 0.01. Children who were not treated continuously during the 6th year of life showed no significant decrease in height. Importantly, the cumulative ICS exposure was not associated with bone mineral content at the age of 6 years in any of the stratified ICS groups.

Despite the statistically significant association between ICS cumulative use and patients' height, the magnitude of the reported effect was minimal. Moreover, the authors stressed in their discussion the reassuring observation that after 1 year of cessation of ICS use, even after several years of previous ICS treatment, there was no significant effect on children's height. These findings support the results of previous studies that demonstrated the loss of negative effect on growth after ICS treatment cessation [3]. In an editorial published in response to Kunøe's study, the potential effect of asthma severity as a confounder was discussed [4]. As asthma severity was not assessed in this observational study, the potential negative effect on growth of a poorly controlled disease by itself should be considered. Specifically, the subgroup of children that have stopped ICS treatment by the age of 5 years and reported stable growth trajectories may reflect the natural improvement in the asthma course.

Most studies so far have evaluated the growth of children with asthma along few years of follow-up at the most, while longer-term longitudinal data are lacking. An important study in twin pairs discordant for asthma [5] has found no significant effect of asthma on height in within-pair analyses, other than a transient effect attributed to a delay in puberty. Genetic factors might act as important confounders, which are difficult to control, in population-based studies.

The second study we discuss here is by Chen et al. where a large UK Biobank data was used to elucidate the influence of childhood asthma on adult height, while considering known genetic heterogeneity in height. The matched cohort study included 13,602 European adults who were diagnosed with asthma before the age of 18 years, compared to 136,008 controls. Overall, childhood asthma was associated with shorter height at adulthood, with an age-dependent trend toward a lower magnitude of association with increased age at asthma diagnosis. Reduction of 2–3% in height among men and women with asthma diagnosed before the age of 7 was observed. Moreover, the height deviation between actual attained height and each person's genetically determined height was only significant in individuals diagnosed with asthma before 4 years of age, with a stronger association among males. The height deficits were observed both in individuals that were treated and were not treated with ICS.

While considering the limitations of this community-based study (including self-reported diagnosis of asthma, missing data, and lack of information regarding symptoms or disease severity), the results suggest a stronger association between asthma and growth mainly in early life period, and highlight the need for more comprehensive longitudinal research as well as clinical surveillance of growth in children diagnosed with asthma.

Evaluation of parameters associated with growth retardation in children with coeliac disease

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Comments: Celiac disease (CeD) is an immune-mediated enteropathy that affects the integrity of the intestinal mucosa and can present with a wide spectrum of signs and symptoms [6]. While the classical presentation of malabsorption and malnutrition was predominant in the past, a substantial proportion of children are currently diagnosed with nonspecific abdominal complaints or without any symptoms [7, 8]. Still, growth faltering and altered weight gain remain common and important parts in CeD presentation [9].

Taskin et al. have described, in this current publication, the prevalence and risk factors for growth retardation in a contemporary cohort of newly diagnosed children with CeD from Turkey. The study included 169 patients (64.5% females), with mean (SD) age at diagnosis of 8.3 (4.4) years. In this cohort, 42.6% presented with growth retardation, defined as height and/or weight below the 5th percentile for age. Vomiting was the only gastrointestinal symptom that significantly correlated with growth retardation at presentation. In this study, longer symptom duration, but not age at diagnosis, had a positive correlation with growth retardation. Interestingly, CeD patients with growth retardation had shorter breastfeeding duration compared to patients without growth retardation; however, no significant correlation was found with the duration of gluten exposure.

This cohort, which included mostly Turkish and some Syrian pediatric patients, demonstrates that CeD may still be accompanied by high rates of undernutrition and growth delay. In this study population, the relatively advanced age at diagnosis and long duration of symptoms (17 months in patients with growth retardation, and 12 months without growth retardation) should be acknowledged. The accessibility of medical diagnosis and care, as well as food security, may be especially important in children with CeD worldwide.

The effect of gluten-free diet on body mass index in paediatric celiac disease

Anafy A[1,2], Cohen S[1,2], Ben Tov A[1,2], Amir A[1,2], Weintraub Y[1,2], Moran-Lev H[1,2], Dali Levy M[1,2], Ankona Bussel M[1,2], Yerushalmy Feler A[1,2]

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Acta Paediatr 2021;110:2233–2239

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https://pubmed.ncbi.nlm.nih.gov/33529351/

Comments: Contrary to the previous paper, it has already been reported over the past decade that overweight and obesity at disease onset is not unusual in children presenting with CeD [10–12]. Moreover, the rates of obesity in patients with CeD (after diagnosis) are rising, as reported recently in an adult population-based study from the USA [13]. Initiation of GFD in newly diagnosed patients can alter body weight and composition in various directions.

This study by Anafy et al. describes patterns of body mass index (BMI) in children with CeD at diagnosis and during follow-up with gluten-free diet (GFD). The study included 236 patients (62% females) with a median age 7.9 years. At diagnosis, the rates of underweight, normal weight, and overweight were 10.1, 76.3, and 13.6%, respectively. Overall, there was no significant change in BMI for the entire cohort, during a median follow-up of 16 months under GFD. However, a significant shift between categories of BMI was observed. Among patients who were overweight at diagnosis, 44.4% reached a normal BMI and 55.6% remained overweight under GFD. Among patients with normal weight at diagnosis, most remained in the same category, while 4.3 and 6.9% became underweight and overweight, respectively. There were no shifts between underweight and overweight categories.

The interesting observations in this study stress the multidirectional changes in nutritional status that can occur in children with CeD after GFD initiation. Although the desired goal of achieving and maintaining normal body weight seems to dominate, the significant changes in diet and habits can potentially cause reduction in weight among children with selective eating, as well as undesired excessive weight gain due to unbalanced diet. The normalization of BMI in a significant portion of children who were overweight at CeD diagnosis may reflect the positive effect of adopting healthier eating practices together with medical and nutritional follow-up. Either way, the important role of dietary and nutritional guidance and continuous follow-up cannot be overstressed in children with CeD.

Pediatric-onset inflammatory bowel disease has only a modest effect on final growth: a report from the epi-IIRN

Assa A[1,2], Assayag N[3], Balicer RD[4], Gabay H[4], Greenfeld S[5], Kariv R[5,10], Ledderman N[6], Matz E[7], Dotan I[8,10], Ledder O[3], Yerushalmy-Feler A[9,10], Turner D[3], Cohen S[9,10]

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J Pediatr Gastroenterol Nutr 2021;73:223–230

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Comments: Growth retardation is common in pediatric inflammatory bowel disease (IBD), mostly in children with Crohn's disease, and is influenced predominantly by the chronic inflammatory process that causes growth hormone (GH) resistance, in addition to malnutrition, malabsorption, and increased nutritional requirements and losses [14]. Although early data have suggested that pediatric-onset IBD negatively affects final height [15], there is a debate regarding the current evidence for final height impairment in the era of improved care and biologic treatments. Recent studies [16–18] report only mild or no decrease in the final height of patients diagnosed with IBD during childhood, with various identified risk factors for delayed growth.

In this study by Assa et al., 2,229 patients with pediatric-onset IBD were identified in an Israeli national database and were matched to 4,338 non-IBD controls. No significant differences were found in final height between males with IBD and matched controls. Females with Crohn's disease were marginally shorter than matched controls corresponding to a mean difference of 0.7 cm. There was no difference in final height for patients with ulcerative colitis, regardless of sex and age at diagnosis. No significant differences were observed in the rates of short stature between cases and controls. Although no significant difference was noted in final height for the entire cohort, when the adjusted mean difference was analyzed there was a significant reduction of −0.43 cm in both sexes. As for treatment with anti-tumor necrosis factor-α, there was no overall significant difference in the change of height *z*-score from diagnosis to adulthood between treated and untreated patients. However, in the subgroup of patients with growth impairment at diagnosis (defined as height *z*-score of <-1) treated with anti-tumor necrosis factor-α, absolute height improvement was significant, with 33% of these patients improving to *z*-score > -1 at the final height.

Overall, this study is in line with the trend of results that appear in recent studies, where despite growth impairment in significant proportion of children with IBD, the effect on final height seems to be modest. This highlights the importance of identifying the subgroup of children with IBD with significant growth impairment, in order to personalize and adjust treatment goals including maximizing growth potential in the short window of opportunity to achieve adequate final height.

Moderate-to-vigorous physical activity is associated with higher bone mineral density in children with inflammatory bowel disease

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J Pediatr Gastroenterol Nutr 2022;74:54–59

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https://pubmed.ncbi.nlm.nih.gov/34321428/

Comments: There is a plethora of data on the effect of IBD on bone mineral density (BMD) as well as different alternation in body composition. However, the interplay between IBD and physical activity is still obscure. While IBD can have a negative effect on physical activity due to fatigue, gastrointestinal symptoms, and altered muscle mass and function, there is growing evidence that physical activity can be beneficial for patients with IBD [19, 20]. A recent study published this year has shown that children and adolescents with mild or inactive IBD have almost similar patterns of daily physical activity compared with healthy control, except for males who had reduced moderate-to-vigorous physical activity (MVPA) [21]. Most patients with IBD, similar to their matched healthy controls, did not fulfill the recommendation of adequate daily MVPA.

In this current study, Trivić et al. aimed to evaluate the relation between physical activity, body composition, and BMD in pediatric patients with IBD in remission. The study included 40 patients with IBD (mean age of 15 years, 60% males, 50% with Crohn's disease). The prevalence of decreased BMD (z-score < -1) in this cohort was 20%. Patients with Crohn's disease had significantly lower BMD and lower lean body mass scores than patients with ulcerative colitis. Physical activity was assessed by a triaxial accelerometer worn over 5 consecutive days. The average time spent in physical activity was 247 min/day, with 46 min/day spent in MVPA. Only 15% of patients fulfilled the WHO's recommendation of 60 min of MVPA daily [22]. The study reported a significant positive correlation between time spent in MVPA, and both BMD and lean body mass z-scores. In a multivariate analysis, only BMD remained significantly correlated with physical activity.

This study emphasizes the great importance of physical activity for BMD in children with IBD who are in remission. The strong correlation between MVPA and an increase in BMD may suggest a potentially valuable modifiable environmental factor that should further be explored in children with IBD.

Body composition correlates with laboratory parameters and disease severity in infants with biliary atresia

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Pediatr Transplant 2022;26:e14208

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Comments: Biliary atresia is the most common cause of cholestatic jaundice in the first months of life. Malnutrition is a major complication of chronic cholestatic liver disease (CLD), particularly in pediatric patients, with multiple factors involved in the pathogenesis [23, 24]. Poor intake is extremely common due to anorexia and recurrent vomiting, which together with the increased energy needs of a hypermetabolic state may lead to malnutrition and growth failure in these patients [25]. Furthermore, malabsorption and maldigestion play a major role in the disease as a result of the decreased bile pool in the bowel limiting fat absorption, as well as chronic enteropathy secondary to advanced portal hypertension. In CLD, the formation of IGF-1 and IGF-BP3 may be reduced, resulting in an impaired GH/IGF-1 axis. The assessment of nutritional status in children with CLD may be challenging, as fluid retention, ascites, and organomegaly make the conventional methods of weight and height measurements inaccurate for nutritional evaluation [24].

In this study by Marderfeld et al., various anthropometric measurements were used to assess malnutrition in 28 infants with biliary atresia treated in the single pediatric liver transplantation center in Israel. Nutritional assessment included dietary intake, serial anthropometric measurements including weight and length, as well as mid-upper arm circumference, and skin-fold thickness. Fat-free mass and fat mass were measured using air displacement plethysmography (ADP). Based on the various measurement tools, malnutrition presented in 32–78% of the visits in this cohort, with the highest prevalence of malnutrition diagnosed using triceps skin-fold thickness. The serum total bilirubin levels and the pediatric end-stage liver disease score were used to assess disease activity, which correlated best with the low mid-upper arm circumference *z*-score. Interestingly, fat-free mass and fat mass measured by ADP did not show any correlations with disease severity parameters. The results of this study recognize the complexity of assessing nutritional status in infants and children with CLD, influenced by the total body water and the mass of enlarged visceral organs. Body composition as measured by ADP, poorly correlated with disease severity, and further studies as well as specific reference values are much needed in this field.

Incidence of and risk factors for short stature in children with chronic kidney disease: results from the KNOW-Ped CKD

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Comments: Growth impairment is common in children with chronic kidney disease (CKD), with a high prevalence of short stature in patients requiring renal replacement therapy during childhood [26, 27]. The etiology of growth retardation in children with CKD may be multifactorial, including genetic factors, delayed puberty, GH resistance, metabolic effect of chronic acidosis, inflammatory process, and malnutrition [28].

This study by Park et al. has evaluated the incidence and risk factors for short stature in pediatric patients with CKD in a large Korean multicenter cohort. The cross-sectional study included 432 children with CKD (median age of 10.9 years, 68% males), who were not on dialysis treatment and did not receive kidney transplantation. The prevalence of short stature and underweight in this cohort was 23 and 14%, respectively. Compared to normative data from Korean general population, children with CKD were shorter and had lower body weight. Recombinant GH (rGH) therapy was administered in only 14.3% of children with short stature in this cohort. Univariable and multivariable regression analyses were performed to examine risk factors for short stature. CKD stages 4 and 5, onset before 2 years of age, underweight, premature birth and low birth weight, and low household income were all identified as independent risk factors associated with short stature in these children.

This study highlights the high prevalence of growth impairment in a large cohort of children with CKD, with important comparisons not only to WHO standards but also to normative data of the specific local population. Notably, only a minority of children with short stature in this cohort received rGH therapy, similar to the results of a recent study from the USA [29], despite an established efficacy of GH treatment in children with renal impairment. Park et al. did not address the prevalence of metabolic acidosis, which is known to be a risk factor for growth impairment in CKD, as was also reported in another study published this year [30]. Nonetheless, of all the risk factors for short stature identified in Park et al.'s study, the authors rightly pointed that under-

weight is the only potentially modifiable one. This emphasizes the importance of strict monitoring of body weight and composition in children with CKD as well as continuous nutritional assessment and management, in order to support adequate growth in this population.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 140–155 (DOI: 10.1159/000527948)

Early Nutrition and Its Effect on Growth, Body Composition, and Later Obesity

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Introduction

A balanced and nutritionally adequate diet in early life is essential for optimal growth and a healthy life both in the short and long term. Many studies are published within this research area. In this review, early nutrition covers infant feeding (mainly breastfeeding), complementary feeding, and nutrition in early childhood with special focus on intake of cow's milk.

We performed a nonsystematic literature search in PubMed using the terms "breastmilk [or] human milk [or] complementary feeding [and] growth [or] body composition." The search resulted in 648 papers of which we selected 12 recent publications published between July 1, 2021 and June 30, 2022. We find these publications of special interest based on their contribution to the research within this field, novelty, and quality. We have divided the papers into 5 topics: human milk appetite-regulating hormones and infant growth (2 papers); early feeding and body composition (3 papers); complementary feeding, growth and adiposity (4 papers); cow's milk, fat and adiposity (2 papers); historical overview of 25 years of research on human milk and lactation (1 paper).

Key manuscripts reviewed for this chapter

Human Milk Appetite-Regulating Hormones and Infant Growth

A review of the relationship between the appetite-regulating hormone leptin present in human milk and infant growth
Juan Castell MF, Peraita-Costa I, Soriano JM, Llopis-Morales A, Morales-Suarez-Varela M
Breastfeed Med 2022;17:98–111

Appetite-regulating hormones in human milk: a plausible biological factor for obesity risk reduction?
Larson-Meyer DE, Schueler J, Kyle E, Austin KJ, Hart AM, Alexander BM
J Hum Lact 2021;37:603–614

Early Feeding and Body Composition

The "drive to eat" hypothesis: energy expenditure and fat-free mass but not adiposity are associated with milk intake and energy intake in 12-week infants
Wells JC, Davies PS, Hopkins M, Blundell JE
Am J Clin Nutr 2021;114:505–514

Early infant feeding effect on growth and body composition during the first 6 years and neurodevelopment at age 72 months
Sobik S, Sims CR, McCorkle G, Bellando J, Sorensen ST, Badger TM, Casey PH, Williams DK, Andres A
Pediatr Res 2021;90:140–147

Infant feeding practices associated with adiposity peak and rebound in the EDEN mother-child cohort
Camier A, Cissé AH, Lioret S, Bernard JY, Charles MA, Heude B, de Lauzon-Guillain B
Int J Obes (Lond) 2022;46:809–816

Complementary Feeding, Growth and Adiposity

Complementary feeding methods – a review of the benefits and risks
Boswell N
Int J Environ Res Public Health 2021;18:7165

Timing of complementary feeding, growth, and risk of non-communicable diseases: systematic review and meta-analysis
Verga MC, Scotese I, Bergamini M, Simeone G, Cuomo B, D'Antonio G, Dello Iacono I, Di Mauro G, Leonardi L, Miniello VL, Palma F, Tezza G, Vania A, Caroli M
Nutrients 2022;14:702

Recommendations on complementary feeding as a tool for prevention of non-communicable diseases
Caroli M, Vania A, Verga MC, Di Mauro G, Bergamini M, Cuomo B, D'Anna R, D'Antonio G, Dello Iacono I, Dessì A, Doria M, Fanos V, Fiore M, Francavilla R, Genovesi S, Giussani M, Gritti A, Iafusco D, Leonardi L, Miniello VL, Miraglia Del Giudice E, Palma F, Pastore F, Scotese I, Simeone G, Squicciarini M, Tezza G, Troiano E, Umano GR
Nutrients 2022;14:257

Complementary feeding caregivers' practices and growth, risk of overweight/obesity, and other non-communicable diseases: a systematic review and meta-analysis
Bergamini M, Simeone G, Verga MC, Doria M, Cuomo B, D'Antonio G, Dello Iacono I, Di Mauro G, Leonardi L, Miniello VL, Palma F, Scotese I, Tezza G, Caroli M, Vania A
Nutrients 2022;14:2646

Cow's Milk, Fat and Adiposity

Cow's milk fat and child adiposity: a prospective cohort study
Vanderhout SM, Keown-Stoneman CDG, Birken CS, O'Connor DL, Thorpe KE, Maguire JL
Int J Obes (Lond) 2021;45:2623–2628

Association of cow's milk intake in early childhood with adiposity and cardiometabolic risk in early adolescence
McGovern C, Rifas-Shiman SL, Switkowski KM, Woo Baidal JA, Lightdale JR, Hivert MF, Oken E, Aris IM
Am J Clin Nutr 2022;116:561–571

Historical Overview

25 years of research in human lactation: from discovery to translation
Geddes DT, Gridneva Z, Perrella SL, Mitoulas LR, Kent JC, Stinson LF, Lai CT, Sakalidis V, Twigger AJ, Hartmann PE
Nutrients 2021;13:3071

Human Milk Appetite-Regulating Hormones and Infant Growth

A review of the relationship between the appetite-regulating hormone leptin present in human milk and infant growth

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Appetite-regulating hormones in human milk: a plausible biological factor for obesity risk reduction?

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J Hum Lact 2021;37:603–614

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Comments: In recent years, hormones in human milk (HM) have been suggested to affect appetite regulation in infants through similar mechanisms as the endogenously produced hormones [1], and thereby affect growth. Leptin is the most investigated appetite-regulating hormone (ARH) and is secreted from the adipose tissue [2, 3]. Endogenously produced leptin affects appetite through receptors in the hypothalamus of the brain, by reducing energy intake (EI) and increasing energy expenditure (EE) [4]. Animal studies have found that orally ingested HM leptin can enter the circulation [5], which makes the hypothesis biologically plausible. However, evidence on the influence of HM ARH on infant growth is sparse and the high risk of confounding in observational studies limits the ability to infer causality and draw conclusions. We found 2 studies addressing these issues.

Castell et al. reviewed the current literature within the area of HM leptin and infant growth outcomes with the posed hypothesis that HM leptin affects appetite regulation and thereby growth. They studied 18 papers, including both original research and other reviews, published from January 1, 2015 to December 31, 2019. The studies were mainly observational cohort studies with sample sizes ranging from $n = 20$ up to $n = 350$. Two of the original research papers presented relationships between HM leptin concentrations and infant weight [6, 7] and/or body composition, although results were slightly conflicting. Brunner et al. measured HM leptin at 6 weeks and 4 months and infant anthropometric measurements were collected at birth and at 6 weeks, 4 months, and at 1 and 2 years. They found inverse associations between HM leptin and infant weight and lean body mass at 4 months, but not at later time points. This might suggest that appetite regulation is more likely to affect fat-free mass (FFM) accretion rather than fat deposition during breastfeeding. Leptin in HM declined across lactation; thus increased concentrations in early lactation might be driving the association. The other study, by Nuss et al., found that HM leptin inversely correlated with infant growth measures such as weight and fat mass (FM) percentage at 4 to 8 weeks postpartum, but only in infants of mothers with normal weight compared to overweight [7]. This suggests an effect on deposition of fat compared to lean mass, which is contrary to the findings by Brunner et al.

The review also presents studies investigating the association between infant plasma leptin and growth depending on feeding practice. One of the studies found higher plasma leptin in breastfed infants compared to formula-fed infants [8], which could reflect either orally ingested HM leptin or increased endogenous production of leptin. Conversely, Breij et al. found higher serum leptin in formula-fed infants compared to breastfed infants [9] and serum leptin correlated furthermore positively with infant FM percentage. One of the main limitations is the lack of evidence regarding absorption of the hormones in the infant gut. As such, we cannot determine that HM leptin

is the main contributor to circulating levels of the hormones and/or for associations seen with infant growth.

The results from this review overall emphasize the conflicting evidence within this area. The studies diverge in several important aspects including method of milk sample collection, sample size, and study design, which increases the risk of bias and complicates comparison. Other factors could be of importance when investigating the associations between HM hormones and infant outcomes such as infant milk intake (MI) or bacterial colonization [10].

The study by Larson-Meyer et al. investigates the hormones leptin, peptide YY (PYY), glucagon-like peptide 1 (GLP-1), and ghrelin in HM. They further pose 3 aims of their study, namely, to investigate (1) the hormone concentrations across lactation from 1 to 6 months, (2) maternal predictors of the hormones in HM, and (3) the associations between HM hormones and infant growth. They use a combination of fore- and hindmilk and have a sample size of $n = 22$ mothers at 1 month and $n = 15$ at 6 months. They found declining concentrations of milk fat as well as leptin, ghrelin, and PYY from 1 to 6 months of lactation. Furthermore, milk fat and leptin were positively associated with maternal body mass index (BMI), which is also supported in the literature [11]. Lastly, the authors found that milk fat in foremilk at 1 month positively associated with weight-for-age *z*-score, whereas GLP-1 and leptin at 1 month were negatively associated with weight-for-age *z*-score at 6 and 12 months, respectively. The authors mention that the associations seen between milk fat and maternal adiposity might be driven by a few mothers with obesity whose milk could contain higher fat concentrations. As leptin is partly secreted by the adipose tissue, HM leptin might correlate with milk fat and could mask associations between HM fat and infant outcomes. These results illustrate the complexity of this research area, as we cannot elucidate whether genetic disposition for obesity is the true predictor for infant weight. Furthermore, the authors chose a foremilk and a hindmilk sample, which may not represent a complete feed, and concentrations of milk fat and/or leptin might be either over- or underestimated compared to the infant's actual intake.

In conclusion, the area of HM hormones is still controversial. This, however, does not make the field of research less important, only challenging for the researchers. Statistical analyses and the resulting conclusions have to be made carefully and with respect to relevant limitations.

The "drive to eat" hypothesis: energy expenditure and fat-free mass but not adiposity are associated with milk intake and energy intake in 12-week infants

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Am J Clin Nutr 2021;114:505–514

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Comments: In this reanalysis of previously collected data, Wells et al. explored the drive-to-eat hypothesis among 48 infants at 12 weeks of age. The hypothesis posits that rather than FM and associated adipokines working to maintain energy balance through appetite alterations, appetite instead adapts as a function of EE and accordingly FFM.

Participants were predominantly breastfed (n = 24) or formula-fed (n = 24), healthy, full-term infants who had participated in a British study to investigate energy metabolism. Intake of supplementary foods was minimal though was permitted after 11 weeks. MIs were estimated by test-weighing of the infant or bottle over two 24-h periods and EI was estimated.

Body composition and EE were measured with deuterium dilution and dilution spaces calculated via back-extrapolation. The sleeping metabolic rate (SMR) was measured as a proxy for, and in place of, the basal metabolic rate using a Deltatrac MK1 metabolic monitor measuring respiratory gas exchange.

Pearson's correlations showed that MI and EI were positively correlated with FFM but not FM, while also being positively correlated with SMR and EE. As a tissue with greater metabolic activity, FFM but not FM was correlated with SMR and EE. Spearman's correlations showed that MI and EE were positively correlated with weight gain over the 1-week data collection period, but EI was not. In multiple regression models adjusted for mid-parental height, MI was associated with SMR independent of FFM, but FFM was not significantly associated with MI in the same model. In a further model, EE and FFM were both independently associated with MI. When investigating EI instead of MI, FFM was independently associated in models including either SMR or EE, which were each independently associated with EI.

These results support that MI and EI appear to match FFM and EE in infants, but not FM. This finding is new in infants and suggests that adipose-derived hormones, a front-running theory in infant satiety and appetite regulation, may not necessarily function as in adults. This study provides a glimpse at the "other side of the coin" of infant growth and reminds us that reverse causality should always be considered, i.e., perhaps the infants with greater MI grow faster, or perhaps the faster growth stimulates greater MI. It is also worth highlighting the significance of mid-parental height when included in the models to account for a heritability of growth-drive. That this appears to influence infant MI, EI, and weight-gain suggests a stimulatory effect on

appetite that can be incorporated into future studies investigating appetite regulation.

This investigation had strong methodology throughout, with precise measures of body composition and EE using a reference technique. The assessment of SMR in infancy is also something seldom seen in the field of infant feeding so brings a novel aspect to the discussion of infant appetite drive.

Early infant feeding effect on growth and body composition during the first 6 years and neurodevelopment at age 72 months

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Pediatr Res 2021;90:140–147

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https://pubmed.ncbi.nlm.nih.gov/32961547/

Comments: This study assessed differences in growth and body composition longitudinally over the first 6 years between infants fed with breastmilk (BF), soy-based formula (SF), or cow's milk-based formula (MF) from 3 to 12 months.

A large sample of 600 healthy, term-born infants were recruited between ages 1 and 2 months. Parents had chosen which diet their infant was to follow before enrolling, and were excluded if this choice changed between 2 and 12 months or if they introduced complementary foods before 4 months. The formula groups were provided with appropriate formula to strengthen adherence and standardize formulations. Within the breastfeeding group, half breastfed until 12 months, a quarter weaned to formula between 9 and 12 months, and the remaining quarter weaned to formula before 9 months. Growth assessment took place at 3, 6, 9, 12, 24, 36, 48, 60, and 72 months, which included body composition measurements via dual-energy X-ray absorptiometry (DXA). Complementary food was recorded by completion of 3-day food records.

The final analysis contained 178 BF, 179 MF, and 169 SF infants. There were some feeding-group differences at baseline, which we would expect as the groups were not randomized; gestational age, birthweight, maternal IQ, and parental education were all higher in the BF group.

At each time point from 24 to 72 months, infant BMI was lower in the BF group compared to the SF group. At 9 and 12 months, BF infants were around 0.5 kg lighter than both MF and SF infants. At measurements from 36 to 72 months, BF infants were 3–4 kg lighter than SF infants. At 6, 9, and 12 months, BF infants were shorter than both groups of formula-fed infants. Fat mass index (FMI) was higher in BF infants compared to SF infants at 3 and 6 months, which reversed at 36 and 48 months, when FMI was higher in the SF children. At 60 and 72 months, BF children had lower FMI compared to both SF and MF children. BF infants tended to have lower fat-free mass index (FFMI) than formula-fed infants up to 6 months, after which we expect complementary feeding (CF) to begin contributing to growth variation. Interestingly, FFMI was higher in SF children at 36 and 72 months by 0.3–0.4 kg/m^2 compared to MF, a result which

could arise from the differences in length. Possibly contributing to some of these differences was the observed lower EI in BF infants in the first year versus formula-fed infants. This could be seen as lower EI in the BF group contributing to reduced FFMI or, following from the paper by Wells et al. commented on above, as a greater drive-to-eat due to the higher FFMI in formula groups.

The longitudinal approach and reference body composition technique in DXA represent great strengths of this study. Furthermore, the impressive sample size is larger than many studies we see in this area. The lower BMI observed in BF infants is a familiar result and supports previous research indicating a protective effect of breastfeeding against obesity. This characteristic of higher FMI and lower FFMI of breastfed versus formula-fed infants in infancy supports to the hypothesis that higher-protein formula feeding can indeed influence body composition at this age and can switch direction of association into later childhood. This study also makes the important observation that SF feeding does not result in unfavorable changes to infant body composition when compared to MF, although breastfeeding remains optimal.

Infant feeding practices associated with adiposity peak and rebound in the EDEN mother-child cohort

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Int J Obes (Lond) 2022;46:809–816

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https://pubmed.ncbi.nlm.nih.gov/34980907/

Comments: Later age and higher magnitude of infant BMI peak, also called adiposity peak (AP), and younger age when BMI starts to increase again, called adiposity rebound (AR), have been associated with the risk of obesity in many studies. This study is based on the French Eden cohort and the study included 1,225 children. Data on infant feeding practice were collected at birth and 4, 8, and 12 months and growth pattern was modeled on growth data from the child's health booklet up to 12 months. Mean age for AP was 9.9 months and for AR 5.5 years. Interestingly, this study found that child sex had a moderating effect on the association between infant feeding and AP and AR. For boys, longer breastfeeding duration was related to a reduced BMI at AP, which is associated with a lower risk of adiposity later in childhood. Later age at AR was associated with duration of breastfeeding in girls, but in boys it was associated with delayed introduction of complementary foods. This study highlights how infant sex plays an important role in the association between early nutrition, growth, and later risk of obesity and thereby underlines that infant sex should be included in future analysis of how early nutrition is affecting growth.

Complementary feeding methods – a review of the benefits and risks

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Comments: While there are several aspects and types of CF methods, this paper focuses only on baby-led weaning (BLW). Twenty-nine studies of BLW were reviewed and the authors conclude that there is suggestive evidence that BLW can reduce food fussiness and improve satiety responsiveness, but the results are far from conclusive. The potential negative effects of BLW are choking and underweight, but there is no evidence to support such effects. BLW can in theory reduce the risk of overweight, but only a few of the included studies have examined this. These studies lean toward BLW reducing the risk of overweight. The author concludes that there is a need for more high-quality studies examining the effect of BLW on growth.

Timing of complementary feeding, growth, and risk of non-communicable diseases: systematic review and meta-analysis

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Recommendations on complementary feeding as a tool for prevention of non-communicable diseases

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Nutrients 2022;14:257

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Complementary feeding caregivers' practices and growth, risk of overweight/obesity, and other non-communicable diseases: a systematic review and meta-analysis

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Nutrients 2022;14:2646

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Comments: During the year covered by this review, a large group of Italian researchers have published 3 papers on CF in the journal *Nutrients*: 2 systematic reviews and meta-analyses and 1 concept paper. The 3 papers focused on different aspects of the effects of CF on growth, risk of overweight, and other noncommunicable diseases (NCDs).

The focus of the systematic review and meta-analysis by Verga et al. is how the timing of CF affects growth and risk of NCDs. They compared start of CF between 4 and 6 months with start at 6 months and the outcomes were growth at 12 months, overweight/obesity at 3–6 years, and iron status. They could only identify 7 studies addressing these issues, and none of them found significant differences on these outcomes. They therefore conclude that the review supports recommendations from the WHO and the EFSA (European Food Safety Authority), namely, that there is no advantage of introducing CF before the age of 6 months.

The systematic review and meta-analysis by Bergamini et al. investigate how caregiver CF practices affect infant growth, overweight/obesity, risk of choking, dental caries, and risk of NCDs. They included several feeding practices: studies on BLW and responsive CF where the active behavior of the child is prioritized; studies on a modified special version of BLW called Baby-Led Introduction to SolidS (BLISS), where infants at each meal are offered 3 different foods, rich in iron, energy, or fiber; studies examining the effects of nonresponsive CF, where the caregivers are overly active (forcing) or overly passive in relation to feeding of the infant. The authors' overall assessment of the evidence from the few randomized controlled trials included was that it was low. They concluded that it was not possible to state that either BLW or BLISS had a preventive effect on later overweight. However, they concluded that responsive feeding can result in lower incidence of overweight/obesity and that nonresponsive feeding can lead to either excess weight or lower weight.

The concept paper by Caroli et al. contains recommendations on CF from a working group with members from several Italian scientific societies with expertise in pediatric nutrition. The paper presents 38 specific recommendations on CF. For each of these recommendations, it is stated if it is an expert opinion, or if the evidence is weak or strong. The panel consensus is also mentioned, and it differs between 100% for many of the recommendations, down to 75% consensus. Among the 38 recommendations are the following: protein intake should not exceed 14% of total EI for children between 6 and 24 months old; CF should not be introduced before 6 months in breastfed and formula-fed infants, if the infants are growing well; unmodified cow's milk should not be given before 12 months and from 12 to 24 months it is suggested to use formula, as an alternative to cow's milk to limit protein intake. Furthermore, the amount of cow's milk, if given, should be less than 500 mL (panel consensus only 75%) and it is suggested not to use BLW. The concept paper also mentions important research areas where more evidence is needed, e.g., age and time window when a specific nutrient may act as trigger for a programming effect, and the impact of CF feeding styles like BLW and responsive and nonresponsive feeding.

Last year, *Nutrients* published a paper authored by some of the same Italian authors discussing if breastfed and formula-fed infants need different CF [12]. One of the main focuses of the paper is protein intake and type of milk offered to the child. The authors suggest that the advice for CF should differ between breastfed and formula-fed infants, mainly to prevent a too high protein intake in formula-fed infants. Thereby they go against the advice from ESPGHAN, i.e., that the recommendations should be the same independently of feeding practice to avoid confusion for the parents [13]. They also suggest that during the second year (12–24 months), what they call young child formula can be used to meet the age-related nutrient requirements. In a recent paper by Lutter et al. [14], it is stated that what they call follow-up formula and growing-up milks is deemed unnecessary and not recommended by the WHO and many pediatric societies.

Cow's milk fat and child adiposity: a prospective cohort study

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Int J Obes (Lond) 2021;45:2623–2628

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https://pubmed.ncbi.nlm.nih.gov/34433906/

This article is also reviewed in the chapter by Shalitin and Giannini [this vol., pp. 47–69].

Association of cow's milk intake in early childhood with adiposity and cardiometabolic risk in early adolescence

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Am J Clin Nutr 2022;116:561–571

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https://pubmed.ncbi.nlm.nih.gov/35441227/

Comments: Overweight and obesity in childhood have been of major concern as they often track into adulthood and are difficult to reverse. Therefore, it is essential to have valid and updated strategies and recommendations to prevent overweight and obesity already in childhood. Cow's milk is a main food offered in early childhood and widely consumed in western countries. According to the "early protein hypothesis," high amounts of early protein would stimulate growth, especially fat tissue, which could lead to later increased risk of obesity [15]. Therefore, whole cow's milk is generally first recommended to be introduced at the age of 12 months [16, 17]. However, at the age of 2 years it is recommended to switch to lower-fat cow's milk to reduce the EI and consequently minimize the risk of excess weight gain [18, 19].

Until lately, dairy fat was often considered to have negative effects on young children. However, more recent studies have found that milk and dairy product consumption was neutral or inversely associated with adiposity in children and adolescents [19]. Previous studies investigating the influence of fat content of cow's milk consumed in

early childhood and later risk of overweight and obesity have shown conflicting results and often have important limitations such as lacking adjustment for potential confounders [19–21]. We have selected 2 publications examining the associations between intake of cow's milk fat in early childhood and risk of later adiposity. They give an important contribution toward understanding the relationship between the fat content in cow's milk consumed in early childhood and later risk of overweight and obesity. They both included subjects from prospective cohort studies and adjusted for salient potential confounders.

In a recent study by Vanderhout et al., the associations between intake of cow's milk fat and child adiposity measured as BMI *z*-score (*z*-BMI) among healthy children were examined. They included 7,467 children in the age range from 9 months to 8 years from a Canadian cohort who reported intake of cow's milk. Of these, 4,699 had repeated measurements. The intake of cow's milk fat given as skim (0.1%), 1%, 2%, and whole (3.25%) milk was collected by dietary questionnaires completed by the parents, and milk consumption was also categorized as either whole milk or reduced-fat milk (0.1–2%). The outcome was *z*-BMI, and overweight and obesity were defined according to the WHO criteria for children older than 5 years, as *z*-BMI scores >+1 and >+2 SD, respectively, and applied for all children across ages for consistency. Relevant covariates included inter alia volume of cow's milk and sugary drinks, duration of breastfeeding, parental characteristics, and birth weight. Mean age at baseline was 2.6 ± 1.5 years and mean intake of cow's milk was 475 ± 300 mL/day. At baseline, most children (56%) consumed whole milk whereas 34, 8, and 3% of the children consumed 2, 1, and 0.1% milk, respectively. Mean time for follow-up was 2.7 ± 1.7 years. Information regarding breastfeeding, CF, and parental characteristics was obtained from the parents by standardized questionnaires. They found that an increase of 1% in fat content of the milk consumed corresponded to 0.05 lower *z*-BMI also when adjusting for potential confounders. This result was supported by comparing children consuming whole cow's milk to children consuming reduced-fat milk. The children who consumed whole cow's milk had 16% lower odds of overweight and 18% lower odds of obesity at follow-up compared to children consuming reduced-fat milk.

These findings, which challenge the recommendation of consumption of reduced-fat milk from age 2 years, are supported by the study by McGovern et al. They investigated the associations between consumption of cow's milk (fat content and frequency) in early childhood and adiposity and cardiometabolic risk in adolescence. In this study, 796 children from a prospective cohort established in Boston consuming cow's milk were included. The intake of cow's milk fat given as whole milk, 2%, 1%, and skim milk was collected at baseline. In addition, the frequency of MI was assessed. Outcomes were measures of body composition in early adolescence and included i.a. *z*-BMI and overweight or obesity defined as *z*-BMI ≥ 85th percentile using CDC growth references. Furthermore, body FM was assessed by bio-electrical impedance (BIA) analysis and lean mass, total fat, and trunk FM by DXA. Covariates included, among others, parental characteristics, sex, birthweight, breastfeeding duration, EI and sugary drinks, and *z*-BMI in early childhood. The mean age at baseline and follow-up was 3.2 and 13.2 years, respectively. Most children consumed whole or 2% milk (30.8 and 32.4%, respectively) and 26.5 and 10.3% of the children consumed 1% or skim milk, respectively. MI in early childhood was estimated as frequency (mean 2.3 ± 1.2 times/day). They compared the intake of milk with higher fat content (whole milk and 2%) versus intake of milk with reduced fat (1% and skim milk) for the outcomes measuring early adiposity in different models with adjustment for increasing number of covariates. They found that intake of higher-fat milk compared to lower-fat milk was associ-

ated with lower adiposity for all body composition techniques in models adjusted for most covariates. However, when adjusting for *z*-BMI at baseline and change in *z*-BMI from 2 to 3 years, only overweight or obesity remained significant, corresponding to 40% lower odds of overweight or obesity in early adolescence for children who consumed high-fat milk compared to children consuming low-fat milk in early childhood. Frequency of MI in early childhood was not associated with adiposity and neither frequency nor fat content of intake of cow's milk was associated with cardiometabolic risk in adolescence.

The 2 studies both showed that intake of low-fat milk in early childhood was not associated with reduced risk of overweight or obesity later in life, but suggested that an inverse relationship might exist. The follow-up periods in the studies were different. The study by Vanderhout et al. had a relatively short mean follow-up time, which is insufficient to evaluate long-term effects. However, they applied a longitudinal design as many of the children had repeated measures. BMI was used as outcome in both studies but is not a direct measure of body composition. To manage this, McGovern et al. also used DXA and BIA to assess body composition showing the same trends and directions as for *z*-BMI. Dietary registrations had limitations in both studies, where MI was not assessed in the study by McGovern et al., and total EI was missing in the study by Vanderhout et al. A strength of both studies was the inclusion of important covariates in the models reducing the risk of confounding which is very important, as families following the dietary guidelines generally may be more prone to follow other health advice. In addition, the risk of reverse causality is relevant to consider, i.e., leaner children may be offered higher-fat milk by the parents and vice versa. Both studies agree that the findings are not sufficient to alter the recommendation for fat content in cow's milk consumed in early childhood. Future studies should include randomized trials to establish any causal relationship between cow's milk fat consumed in early infancy and later adiposity.

Historical Overview

25 years of research in human lactation: from discovery to translation

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Nutrients 2021;13:3071

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https://pubmed.ncbi.nlm.nih.gov/34578947/

Comments: Geddes et al. have published an impressive review, which builds on the research output from the group investigating research on HM and lactation at the University of Western Australia. Twenty-five years ago, Peter Hartmann established this research unit, now called the Geddes Hartmann Human Lactation Research Group. He is the last author of the review. He died in 2021, 80 years old.

The review conceptualized a biological framework on how maternal and infant factors influence HM composition, and how it is related to infant growth, development, and health. It is a very comprehensive review with 46 pages and 337 references. It covers a broad range of topics from breast anatomy, milk secretion, physiology of milk removal, and milk composition to infant intake, growth, body composition, and health. Among the many details included in the review are 5 interesting figures showing the possible pathways of lactocrine programming of the infant. The figures show how maternal body composition is influencing milk components and how these components influence appetite control and body composition. The 5 groups of milk components are proteins, immune factors, appetite hormones, glucocorticoids, and carbohydrates. This review underlines the importance of a broad range of findings emerging from this research group through the past 25 years.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

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Published online: March 22, 2023

Shamir R, Koletzko B, Phillip M, Turck D (eds): Nutrition and Growth. Yearbook 2023. World Rev Nutr Diet. Basel, Karger, 2023, vol 126, pp 156–163 (DOI: 10.1159/000527922)

Pregnancy: The Impact of Maternal Nutrition on Intrauterine Fetal Growth

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Introduction

This chapter of the 2023 edition of the *Yearbook on Nutrition and Growth* reviews important manuscripts published between July 2021 and June 2022 addressing the association of maternal nutrition during pregnancy and intrauterine fetal growth. In the current edition, 8 studies with high impact were chosen, most of which were human clinical trials. In the center of attention were studies that not only showed the associations of maternal malnutrition and abnormal fetal growth but also addressed changes reflected by the placenta. Despite the importance of human studies in this field, animal studies are not to be overlooked as they pave the way for future human studies in fields with scant medical evidence. Hopefully, this chapter will spark enthusiasm in health care providers and researchers to design future studies addressing this important topic.

Key articles reviewed for this chapter

Human Studies

Maternal plasma lipids during pregnancy, insulin-like growth factor-1, and excess fetal growth
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Short-term fetal nutritional stress and long-term health: child height
Karimi SM, Little BB, Mokhtari M
Am J Hum Biol 2021;33:e23531

Maternal and placental zinc and copper status in intra-uterine growth restriction
Yücel Çelik Ö, Akdas S, Yucel A, Kesikli B, Yazihan N, Uygur D
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Mol Nutr Food Res 2021;65:e2100301

Maternal plasma lipids during pregnancy, insulin-like growth factor-1, and excess fetal growth

Chen KY[1], Lin SY[2], Lee CN[2], Wu HT[3], Kuo CH[4,5], Kuo HC[5], Chuang CC[5], Kuo CH[6,7], Chen SC[8], Fan KC[9], Lin MW[2], Fang CT[10], Li HY[11]

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J Clin Endocrinol Metab 2021;106:e3461–e3472
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Comments: This 2-stage clinical study was aimed to explore the association between maternal plasma lipids and excess fetal growth. In the first part of the study, the authors observed higher rates of triglycerides (TG), fatty acids (FA), and insulin-like growth factor-1 (IGF-1) in pregnant women with large for gestational age (LGA) fetuses. In the second and more interesting part of the study, cell cultures were used to show that the addition of several FA to human trophoblast cell lines results in higher IGF-1 mRNA formation. The strengths of the current study lie in the relatively large number of participants. In addition, the fact that both in vivo and in vitro experiments were conducted is also an important addition to the existing literature in this field. As previous studies showed associations between FA and TG levels and LGA, this article stands out in its originality and by showing a direct relationship between FA and IGF-1. From the 4 FA that were studied (linoleic acid, oleic acid, palmitic acid, and stearic acid), only 3 were shown to affect IGF-1 levels. In contrast, in both pregnant women and the placenta models, oleic acid was not associated with fetal growth. Unfortunately, the authors could not find an explanation for this finding. Nevertheless, this observation is promising and can aid in reducing the rate of LGA fetuses and perhaps decrease the rate of small for gestational age babies. By highlighting the major FA responsible for excess fetal growth, this study should be the cornerstone for future studies of clinical nature.

Maternal blood fatty acid analysis reveals similar n-3 fatty acid composition in non-pregnant and pregnant women and their neonates in an Israeli pilot study

Leikin-Frenkel A[1,3], Mohr-Sasson[2], Anteby M[2], Kandel-Kfir M[1], Harari A[1], Rahav R[2,3], Kamari Y[1,3], Shaish A[1,4], Harats D[1,3], Cohen H[1,3], Hendler I[2,3]

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Prostaglandins Leukot Essent Fatty Acids 2021;173:102339

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https://pubmed.ncbi.nlm.nih.gov/34487973/

Comments: This novel observational study set out to compare FA composition between pregnant and nonpregnant women and between mothers and their offspring. Pregnant women had higher levels of saturated FA, monounsaturated FA, and n-6 FA than their nonpregnant counterparts. n-3 FA levels were similar between the groups, and when comparing mothers and their newborn, the latter had a small advantage. Acquiring essential and especially n-3 FA solely from one's diet was suggested to be not sufficient in previous trials. An increased n-3/n-6 FA ratio was shown to be important to fetal growth and was mostly related to neurocognitive development. As pharmaceutical companies and health care organizations suggest the use of n-3 FA supplements during pregnancy, this study succeeds in filling the scientific gap that was lacking. It seems that pregnancy by itself does not pose a risk for a lower n-3 FA levels and even more so, higher levels of n-3 FA are evident in newborn blood, perhaps a sign of efficient placental transfer. The limitations of this study make generalizability difficult. A single blood sample was collected from only a small number of women from a single tertiary center and only at the third trimester and not beforehand. We believe that this study can serve as a pioneer in understanding the role of FA composition in fetal growth. However, larger clinical trials are further needed before final conclusions can be drawn.

Short-term fetal nutritional stress and long-term health: child height

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Am J Hum Biol 2021;33:e23531

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https://pubmed.ncbi.nlm.nih.gov/33155755/

Comments: This study was aimed to explore the impact of in utero exposure to nutritional deprivation during Ramadan (a month of daytime fasting) on height at ages 0–18 for a sample of children from Tehran, Iran. As hypothesized, exposure to Ramadan was associated with shorter stature. The large sample size and the model chosen for measuring the exposure to nutritional deprivation are impressive. We believe it is not only the nutritional deprivation but also the constant metabolic stress that affected fetal growth. Although height at childhood may serve as an indicator of fetal growth, there are other outcomes, such as fetal weight and other anthropometric measures that are

also important in the assessment of fetal metabolic status or the potential in utero deprivation. In addition, although statistically significant, the clinical significance of the approximately 1 cm difference between the groups is questionable. Research done in the field of nutritional deprivation is rare due to ethical reasons. We hope for more studies based on ritual fasting that could advance our understanding on the potential association between the exposure of maternal fasting periods during pregnancy and the long-term growth potential of the offspring.

Maternal and placental zinc and copper status in intra-uterine growth restriction

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Fetal Pediatr Pathol 2022;41:107–115

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Comments: Zinc is necessary for protein synthesis and carbohydrate metabolism and therefore speculated to play an important role in fetal growth. However, studies addressing the association of zinc levels and intrauterine growth are scarce. In the current study, the researchers explored the relation of zinc concentrations in maternal plasma samples as well as in the placentas of normal-weight fetuses and compared the results to those with intrauterine growth restriction (IUGR). Zinc levels in the placenta were lower for those with IUGR. However, no difference was found in maternal plasma zinc levels between the groups. Although limited by small sample size, the current study was a pioneer for the fact that both the placenta and maternal serum levels were sampled for zinc and copper levels, which was not done in previous studies addressing this issue. It seems that it is not the amount of zinc digested that may have an association with IUGR but the amount that eventually reaches the placenta. In addition, the decrease in placenta zinc and zinc/copper ratio levels in the IUGR group may be an indicator for the importance of zinc in fetal development and growth. Finally, placental zinc level correlation with birthweight suggests for the important role of zinc in neonatal development.

Association of the maternal serum albumin level with fetal growth and fetal growth restriction in term-born singletons: a prospective cohort study

Xiong T[1,2], Wu Y[1,3], Huang L[1], Chen X[1], Zhang Y[1], Zhong C[1], Gao Q[1], Hong M[1], Hu X[4], Yang X[1], Yang N[1], Hao L[1]

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Fertil Steril 2022;117:368–375

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https://pubmed.ncbi.nlm.nih.gov/34686372/

Comments: It is well established that serum albumin serves as an indicator for nutritional status in adults and children. In this cohort study from China, the researchers investigated the association of maternal serum albumin levels with fetal growth restriction. A reverse U-shaped relationship between maternal albumin level and birth size was found. The association between a low-protein diet as represented by low albumin levels and fetal growth restriction is not surprising and was addressed in previous studies. However, the current study excelled in its design and size and most intriguing, by the correlation not shown before between high albumin levels and fetal growth restriction. Confounders such as liver disease and inflammatory status were dealt with and even after adjustment, the results remained statistically significant. The exact mechanism for the association of growth restriction with high levels of albumin is yet to be determined and should be assessed in future studies. In addition, the findings of the current study raise the possibility of maternal albumin as a target for maintaining maximum fetal growth potential and preventing fetal growth restriction.

Weight gain rate in the second and third trimesters and fetal growth in women with gestational diabetes mellitus: a retrospective cohort study

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BMC Pregnancy Childbirth 2022;22:424

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https://pubmed.ncbi.nlm.nih.gov/35596164/

Comments: The prevalence of gestational diabetes (GDM) is rising over the past few decades mainly due to the increase in maternal obesity and advanced maternal age at delivery. One of the most important complications of GDM is fetal overgrowth. In the current study, the researchers aimed to define the optimal gestational weight gain goals for

pregnant women with GDM while minimizing the rates of LGA newborns and macrosomia. As expected, the rate of LGA and macrosomia was associated with weight gain rate in the second part of pregnancy. However, there was no association between weight gain and small for gestational age newborns. Thus, raising the bar for a stricter diet, especially for overweight or obese women with GDM, should be considered for the prevention of fetal overgrowth. When trying to control weight gain in women with GDM, one must keep in mind that the diagnosis of GDM is usually made at the late second or the third trimester. Therefore, there is a narrow time frame remaining for the lifestyle and dietary modifications. Instead, it may be more clinically effective to allocate pregnant women at risk of GDM for potential intervention with strict diet early in gestation if proven effective in future well-designed prospective observations.

Animal Studies

Maternal high-fat diet during pregnancy with concurrent phthalate exposure leads to abnormal placentation

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Sci Rep 2021;11:16602

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Comments: The major determinant of fetal growth in mammals is nutrient delivery via the placenta, which occurs primarily by transporter-mediated mechanisms and diffusion. Transport of nutrients in the placenta is dependent on many factors, including placental size, morphology, transporter capacity/availability, and placental blood flow, among others. In this study, the researchers demonstrated the combined effect of a high-fat diet and phthalate exposure on placentation and fetal growth. Phthalate exposure along with a high-fat diet had a detrimental effect on placental vasculature and regulation as expressed by low PAPP-A levels and PPARγ function. This fascinating research is the first to be done with environmentally relevant levels of phthalate exposure. Although previous studies showed a tremendous negative effect on fetal growth, most of them were flawed due to exposure levels much higher than the average human exposure.

This study also indicates that the combined exposure to high-fat diet and phthalate suppresses the expression of key PPARγ target genes, which mediates placental functions. It would be interesting to explore the association of high-fat diet with concurrent phthalate exposure and the risk of clinical expression of placental complications such as hypertensive disorders of pregnancy and placental abruption. Nevertheless, the results of the current study provide novel insight into potential etiological factors underlying pathological placentation, which are among the leading causes of maternal and fetal morbidity and mortality.

Maternal exposure to oxidized soybean oil impairs placental development by modulating nutrient transporters in a rat model

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Mol Nutr Food Res 2021;65:e2100301

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Comments: While most of nutritional studies focused on beneficial supplements affecting fetal growth, the current study was conducted to understand the notorious effects of oxidized lipids on the placenta.

The results of the current study imply that dietary oxidized soybean oil (OSO) treatment dramatically decreased the weights of the placenta and the embryo and adversely affected the growth and development of the placenta. Moreover, this study also found that OSO treatment significantly increased the coefficients of the liver and kidney in gestational rats. On day 20 of gestation of female rats, OSO was associated with decreased placental and embryonic weights as the oxidative degree increased in a linear manner. This effect was also shown in biochemical and pro-apoptotic markers. The formation of free radicals and their inflammatory effect is well known. However, the effect on placental development was less clear prior to the current study. As soybeans are commonly consumed worldwide, the results of the current study warrant special attention regarding the handling and consumption of soybeans during gestation, especially if others will support findings of this study.

Overall Commentary

Maternal nutrition affects fetal growth in various mechanisms. Nutrient supplementation during pregnancy and maintaining balanced maternal diet may improve placental function and consequently offspring's outcome. However, the impact of nutrition on fetal/offspring growth and development is attenuated by genetic, demographic, behavioral, and other factors. Thus, it should be personalized to achieve its maximal benefit.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding.

Author Contributions

All authors have read and commented on the reviewed manuscripts.

Author Index

Subject Index

RESEARCH

World Review of Nutrition and Dietetics

Editor
B. Koletzko

ISSN
0084–2230

Nutrition and Dietetics

Women's and Children's Health

Endocrinology

126 **Nutrition and Growth:** Yearbook 2023

Editors: R. Shamir, Petah Tikva/Tel Aviv; B. Koletzko, Munich;
M. Phillip, Petah Tikva/Tel Aviv; D. Turck, Lille
X + 186 p., hard cover, 2023.
ISBN 978–3–318–07056–9

A complex variety of factors affect linear growth, weight gain, and body composition, with nutrition being one of the most important contributors. However, the mechanisms through which nutrition affects growth is not completely understood. This publication focuses on the interplay between nutrients and the endocrine system via manuscripts describing different clinical conditions and diagnoses covering various aspects of nutrition and growth.

As in the previous volumes of the Nutrition and Growth Yearbook, an international group of experts in nutrition and growth selected limited number of significant peer-reviewed papers that were published between July 2021 and June 2022. All of the papers are supplemented with editorial comments which aim to serve as "food for thought".

This publication provides an important contribution in examining the relationship between nutrients and the endocrine system. The authors hope that their selections and comments will increase the interest among healthcare providers and researchers in the field and lead to more research in this area.

125 **Nutrition and Growth: Yearbook 2022**

Editors: M. Phillip, Petach Tikva/Tel Aviv; D. Turck, Lille;
R. Shamir, Petach Tikva/Tel Aviv; B. Koletzko, Munich
X + 190 p., hard cover, 2022.
ISBN 978–3–318–07041–5

124 **Pediatric Nutrition in Practice**

3rd revised edition
Editors: B. Koletzko, Munich; Co-Editors: Z.A. Bhutta, Toronto, ON/Karachi;
W. Cai, Shanghai; M.A. Dhansay, Cape Town; C.P. Duggan, Boston, MA;
M. Makrides, North Adelaide, SA; M. Orsi, Buenos Aires
XVIII + 458 p., 64 fig., 45 in color, 124 tab., hard cover, 2021
ISBN 978–3–318–06295–3

123 **Nutrition and Growth: Yearbook 2021**

Editors: R. Shamir, Petach Tikva/Tel Aviv; B. Koletzko, Munich; D. Turck, Lille;
M. Phillip, Petach Tikva/Tel Aviv
X + 166 p., hard cover, 2021. ISBN 978–3–318–06927–3

Karger

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